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(54) Title: PROLYLENDOPEPTIDASE INHIBITORS

(57) Abstract

The present invention relates to new prolylendopeptidase inhibitors of general formula (I).

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PROLYL ENDOPEPTIDASE INHIBITORS

The present invention relates to new compounds of the general Formula (I), to pharmaceutical compositions containing them, and to the process for the preparation of these compounds. A further aspect of our present invention is the use of the new compounds of the general formula I for the treatment of CNS diseases by inhibition of certain enzymes described later on on this page.

Because of the incidence and social consequences of diseases of the central nervous system accompanied with amnesia, dementia and the progressive decline of cognitive and intellectual functioning for example Alzheimer disease, AIDS dementia, senile dementias of various origin (hypoxia, ischaemia) there are significant demands for new pharmaceuticals for treating and preventing the diseases mentioned above.

Prolyl endopeptidase PE or PEP is a post-proline cleaving enzyme (PPCE). It is widespread in mammalian species and can be found in various organs of the body. The level of the enzyme is the highest in the brain, testis and skeletal muscle (Yoshimoto T., Ogita K., Walter, R., Koida M. and Tsuru D.: Biochim. Biophys. Acta, 569, (1979), 184-192).

PEP has some important role in memory process due to the fact that its substrates are biologically active neuropeptides (substance P, thyrotropin-releasing hormone, Arg^8-Vasopressin). These neuropeptides exert characteristic pharmacological effects on the central nervous system: they are capable of changing the performance of animals and humans in learning and memory tasks (Toide K., Iwamoto Z., Fujiwara T., and Abe H.: J. Pharm. Exp. Therapeutics, 274, (1995),1370-1378; Riedel W.and Jolles J., Drugs & Aging , 8, (1996), 245-274). The neuropeptide sustance P prevents β-amyloid-induced neuronal loss and expression of Alz-50 proteins in cerebral cortex (Kowall N.,Beal M.F., Busciglio J., and Duffy L.K.: Proc. Natl. Acad. Sci., 88, (1991), 7247-7251). In brains of patients with Alzheimer's disease, it is well known that the cerebral ACh content decreased and the cerebral function suffers severe

damage (O'Leary R. and O'Connor B.: J. Neurochem., 65, (1995), 953-963). A PEP inhibitor through the increasing the level of TRH could induce ACh release in the brain which should result in a better cognitive performance. It can be supposed that a highly specific PEP inhibitor could prove to be useful in the treatement of diseases of central nervous system in neurodegenerative illnesses.

The new PEP inhibitor as a new drug would be a

1. nootropic drug having memory enhancing and anti-amnestic effect and could be used in treatement of age-related cognitive decline;
2. neuropotective agent useful in therapy of
   a., acute events (ischemia/hypoxia)
   b., progressive neurodegenerative disorders

-Alzheimer's disease
-AIDS dementia
-Huntington's disease

Senile dementia and Alzheimer's disease become serious and fastly outgrowing problem of the aging population and a PEP inhibitor could be useful for the general treatment of the above mentioned serious diseases.

We set ourselves the task of preparing new PEP-inhibitors displaying advantageous characteristics which could serve as active ingredients of new drugs. By advantages we mean over a strong PEP - inhibitory effect, selectivity, easily transfer through the blood-brain barrier, a long half-life, good oral resorption, enchanced chemical and biological stability and advantageous therepautical profile including lower toxicity and low probability of side effects.

During the synthesis and biological examination of numerous new compounds we found that new compounds of the general formula (I) wherein A means an onefold or manifold substituted or unsubstituted organic cyclic group containing one nitrogen atom with one free valency and optionally one or more further heteroatom selected from a group consisting of nitrogen atom, sulfuratom or oxigenatom, especially a group having the general formula (1), (1a), (2), (2a), (3), (3a), (4), (5), (6), (7), (8), (9), (10), (11a), (11b), (12), (12a), (12b), (13), (13a), (14), (15), (16), (17), (18), (19), (19a), (20), (20a), (21), (22), (23), (23a), (23b), (24), (25), (25a), (26), (27), (28), (28a), (28b), (29), (29a), (30), (31), (32), (32a), (33), (34), (35), (36) - wherein

R means hydrogenatom alkyl group of 1-4 carbon atoms or aryl or aralkyl group of 6-12 carbon atoms;

R^1, R^2, R^3 and R^4 mean independently from each other hydrogen atom, halogen atom, hydroxyl group, straight chain or branched chain alkyl or alkenyl- or alkinyl or alkoxy- or alkenyloxy- or alkinyloxy groups containing 1-6 carbon atoms, nitro-group, amino group, monoalkylamino or monoacylamino group of 1-12 carbon atoms ,dialkylamino- or diacylamino group of 2-24 carbon atoms - where the acyl group is an alkyl, aralkyl, cycloalkyl or aryl type -, cyano group, mercapto group, carboxyl group, esterified carboxyl group of 2-7 carbon atoms, hydroxyalkyl group of 1-6 carbon atoms, acyl group of 1-7 carbon atoms, acyloxy group of 1-7 carbon atoms, phenyl or benzyl group, anilino group, benzoyl group, phenoxy group, benzyloxy group, isocyanato group, isothiocyanato group, alkylthio group of 1-6 carbon atoms, sulfamino or sulfamoyl group, thiocyanato or cyanato group;

R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group phenyl group or alkyl group of 1- 4 carbon atoms or R^5 and R^6 together mean oxo group;

R^7 means alkyl group of 1-6 carbon atoms;

R^8 means hydrogen atom or alkyl group of 1-6 carbon atoms or aralkyl group of 7-10 carbon atoms;

the dotted line means an optional chemical bond;

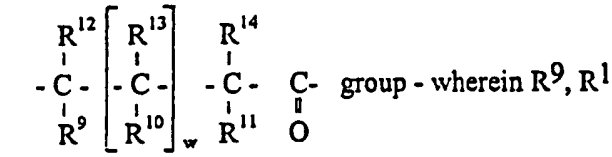
n is zero 1, 2 or 3;

X means-CH_2-group, -NH-group, carbon atom, hydrogen atom, oxygen atom or amino group; or

A means an R` - Y - N = group or R`-Y-N- group - wherein R` means alkyl group of 1-6 carbon atoms, aralkyl group of 7-10 carbon atoms, diphenylmethyl group, alkoxy group , arylalkyloxy group of 7-10 carbon atoms, or phenyl- or phenoxy or phenylalkyl group containing 7-10 carbon atoms or phenylalkyloxy group containing 7-10 carbon atoms optionally substituted with halogen atoms or alkyl groups of 1-4 carbon atoms or nitro groups; Y means chemical bond or oxo-, sulfonyl- or sulfinyl group, R^9 means hydrogen atom or alkyl group of 1-4 carbon atoms; - with the proviso that in the case of formulas (20) and (33) X cannot mean - CH_2- group, - NH- group, oxygen atom or sulfur atom and in the case of formulas (30) and (31) X cannot mean - CH_2- group, oxygen atom or sulfur atom or amino group;

B means $-(CH_2)_m-\overset{\overset{O}{\|}}{C}-$ group - wherein m is an integer of 1 to 21; or

$-O-(CH_2)_p-\overset{\overset{O}{\|}}{C}-$ group wherein p is an integer of 1 to 3; or



group - wherein R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean independently from each other hydrogen alkyl or alkoxy group of 1-6 carbonatoms, halogen, amino group optionally substituted with one or two alkyl group of 1-6 carbonatoms; or

phenyl, phenoxy, aryl-alkyl group of 7-12 carbonatoms or aryl-alboxy group of 7-12 carbonatoms each of them optionally containing 1, 2 or 3 same or different substituents identical to R^1, R^2, R^3 or R^4; or

two of R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean together an oxo or epoxy group or further chemical bond or four of them mean together two further chemical bonds and the remaining groups stand for hydrogen atoms; or

R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean together with the chain carbonatoms a saturated or unsaturated homocycle containing 3-8 carbon atoms or a saturated or unsaturated heterocycle containing 2-7 carbon atoms and a nitrogen or sulfur or oxygen atom, to which optionally an aromatic ring of 6-10 carbon atoms is condensed; and

w is zero or 1;

C means prolyl group or one of the groups of formula (37), (38), (39), (40) or (41) - where n is zero or 1 or 2, Hlg means fluorine, chlorine, bromine, or iodine atom; R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group phenyl group or alkyl group of 1-4 carbonatoms or R^5 and R^6 together mean oxo-group;

R^{16} means an alkoxy group of 1-4 carbon atoms, or $-NH-CH_2-CN$ group, or $-NH-CH_2-CO_2R^7$ group - where R^7 is defined as above; or

D or L structural unit; or one of the group of the formula (42) or (43) or (43a) - where the dotted line means a chemical bond optionally present-, s is 1, 2 or 3 - or a group of the formula (44) -wherein R^{15} means hydrogen atom, alkyl group of 1-6 carbon atoms, phenyl or naphthyl group; or

a group of the formula (45) - wherein Z means NH - group, oxygen atom or sulfur atom;

D means a covalent chemical bond or prolyl- or thioprolyl group, or one of groups of formula (37) or (38), (39), (40) or (41);

L means pyrrolidino- or 2- cyanopyrrolidino, thiazolidino or 2-cyano-thiazolidino or piperidino group optionally substituted with one halogen atom or geminally with two halogen atoms; or

a group of the formula (46) - where R^{17} means hydrogen atom or cyano group, n is 0, 1 or 2 ; or

a group of the formula (47) or (48) or (49); -

and optical , cis-trans, geometric isomers , epimers, tautomers, salts, prodrugs and human and mammalian metabolites of them have significant prolylendopeptidase inhibiting effect and they show one or more advantages mentioned above. Some preferred groups of compounds of the general formula (I) are as defined claimed in claims 3, 8 and 9.

The meaning of „onefold or manifold substituted or unsubstituted organic cyclic group containing one nitrogen atom with one free valency and optionally one or more further heteroatom(s) selected from a group consisting of nitrogen atom, sufuratom or oxigen atom" in case of A covers all know monocyclic or polycyclic group satisfying above definition.

In case of a polycyclic group the rings may be condensed and/or may be in spirocyclic position. Some representatives of above cyclic groups are depicted in formulas, (1), (1a), (2), (2a), (3), (3a), (4), (5), (6), (7), (8), (9), (10), (11a), (11b), (12), (12a), (12b), (13), (13a), (14), (15), (16), (17), (18), (19), (19a), (20), (20a), (21), (22), (23), (23a), (23b), (24), (25), (25a), (26), (27), (28), (28a), (28b), (29), (29a), (30), (31), (32), (32a), (33), (34), (35), (36).

In the definitions of general formula (I) „alkyl group of 1-6 carbonatoms" means a straight chain or branched alkyl group having 1 to 6 carbonatoms such as methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl. The „aryl group of 6-10 carbonatoms" means for example phenyl, tolyl or naphthyl. groups.

The „aralkyl group of 6-10 carbonatoms" means for example benzyl-, 1-phenyl-ethly-, 2-phenyl, ethly-, 1-phenyl-propyl-groups. The alkenyl group of 1-6 carbon atoms means a straight chain or branched alkenyl group such as vinyl, allyl, methaorlyl, crotyl, 3-butenyl, 2-pentenyl-, 4-pentenyl-, 2-hexenyl-, 5-hexenyl. The „alkynyl group of 1-6 carbon atoms" means a straigh-chain or branched alkynyl

group such as ethynyl, propargyl, 2-butynyl-, 3-butynyl, 2-pentynyl, 4-pentynyl, 2-hexynyl 5-hexynyl 4-methyl-2-hexynyl.

The cycloalkyl part of the „acyl group of 1-12 carbonatoms" means for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl group. These definitions may be used in case of alkyloxy, alkenyloxy-, alkymyloxy, aryloxy,aralkyloxy, phenylalkyloxy or alkylamino or acylamino groups.

We have examined the PEP - inhibitory activity and the biological stability of the compounds characterised by formula (I) applying the following methods:

PEP activity measurement on rat brain extract:

After removal of the cerebellum whole brain of male (Sprague-Dawley,180-200g) rats was homogenized in a double volume of 0.1 M Tris-HCl, 1mM EDTA buffer, pH=7.5 (PEP buffer). The homogenate was centrifuged for 30 min. at 4°C at 40000 g and the supernatant, containing the enzyme, was collected. The pellet was resuspended in the same volume of buffer as in the first case and centrifuged again under the same conditions. The two supernatants were pooled and stored in 1ml aliquots at -70°C (for at least 3 months). The supernatant was thawn just before activity measurement and diluted in a 1:15 ratio with PEP buffer. The enzyme activity was measured by using flurometric method described by J. R. Atack et al. (Eur J. Pharmacol., 205, (1991), 157-163). Enzyme reaction was performed at room temperature for 15 minutes in the presence of 62.5 μM Z-glycyl-prolyl-7-amino-4-methyl-coumarin (Bachem Biochem.) as a highly specific synthetic substrate of the PEP. The inhibitory effect of compounds was tested under the same conditions in the presence of 100 to 0.001nM compound. The formation of 7-amino-4-methyl-coumarin was detected spectrofluorometrically at 370 nm exitation and 440 nm emission wavelength. The 50% inhibition concentration of the compounds (IC_{50}) were calculated by curve fitting of the % inhibition of the enzyme versus inhibitor concentration (M) using Hill-equation. IC_{50} values of the compounds of the general formula (I) are in the range of 100nM - 1pM.

Pig brain PEP activity measurement

Purified pig brain prolyl endopeptidase was a kindly gift of László Polgár (Enzymology Institute of the Hungarian Academy of Sciences). Enzyme solution was diluted in the reaction mixture 400000 times. Measurements were performed under the same conditions as in the case of the in vitro measurements on rat brain preparation. The compounds of the general Formula I were shown to be also active on pig brain PEP activity.

In vitro metabolism studies

The biological stability of prolyl endopeptidase inhibitors was studied in mouse , rat and human (preparation of the Central Chemistry Institute of The Hungarian Academy of Sciences) liver microsomal preparation. Mouse and rat livers were pooled and homogenized in 4-fold volume Tris-HCl buffer (pH 7.4) containing 1.15% KCl and 1mM EDTA The homogenates were centrifuged for 30 minutes at 10000 g , the supernatants were further ultracentrifuged for 1 hour at 105000g. Pellets were rehomogenized and ultracentrifugation was repeated. The pellets were re-homogenized again and were diluted with buffer to a final volume of 0.5 g liver/ml. Sample were frozen in 2ml aliquots at -80 °C. Preparations were characterized for cytochrome P450 isoenzyme activities.

New inhibitors of the general formula (I) were tested under the following conditions: Reaction mixture contained 2mg of liver microsomal protein, 0.1M Tris-HCl buffer (pH=7.4), 2mM NADP, 20mM glucose-6-phosphate disodium salt, 10 mM $MgCl_2$ 5 U glucose-6-phosphate dehydrogenase and 50 μM PEP inhibitors in a final volume of 1.5 ml. After 0, 10, 20, 40 min incubation times, reaction was terminated by addition of acetonitrile. Samples were centrifuged at 3000 rpm for 10 minutes. The supernatant was analyzed by HPLC (Supelcosil C18). The unchanged substrate amount was determined and half-life of compounds were calculated.

Some compounds of the general formula I had half-life on human liver microsomes of more than 7 hours. Such good biological stability is in favour of an long lasting effect in vivo and is an advantage over other peptidic-type PEP-inhibitors which are known to be biologically unstable.

The published European Patent Application No 0 232 849 A2 describes numerous PEP-inhibitor including SUAM-1221 (N-[N-(γ-phenyl)butyryl-L-prolyl]pyrrolidine). The compounds of the general formula (I) exert high inhibition activity on prolyl endopeptidase and it is greater than that of above reference compound SUAM-1221 measured in our above described test-system:

Compounds	IC_{50}(M) rat brain extract
Example 123	$2{,}78 \cdot 10^{-10}$
Example 31	$3{,}60 \cdot 10^{-10}$
Example 171	$4{,}51 \cdot 10^{-10}$
SUAM-1221	$3{,}12 \cdot 10^{-8}$

The preparation of compounds of the general formula (I) is carried out by methods well known from the literature or by obvious chemical equivalents thereof relating to the synthesis of peptide type substances.

The A and B units of compounds of the general formula A - B - C - D - L (I) - where the meanings of A , B , C , D , and L are as described above - are coupled by the reaction of the appropriate acid anhydride or other activated acid derivative and an amine, yielding compounds of the general formula (II) - where the meanings of A and B are as described above. The coupling of units C and D happens likewise by coupling the appropriate activated acid derivative e.g. acid anhydride and an amine. The coupling of units CD and L to yield compounds of the general formula (III) - where the meanings of CD and L are as described above - is carried out by reacting the appropriate mixed anhydride and amine resp. ester and metallo - organic compound.

The starting compounds corresponding to units A, B, C, D, and L are commercially available or readily producible by known transformation of them or as described in Chem Pharm. Bulletin 41 (9) p 1583-1588 (1993.)

We have prepared the compounds of general formula (I) by reacting activated derivatives of compounds of the general formula (II) with compounds of the general formula (III) under conditions of amide coupling usual in peptide chemistry. The activated derivatives of compounds having general formula (II) could be e.g. acid chlorides, which can be synthesized by applying halogenating agents (e.g. thionyl chloride). Active esters can be produced by 1-hydroxyl-benzotriazol in the presence

of N,N'-dicyclohexylcarbodiimid (Chem. Ber. 103, 788/1970/). Mixed anhydrides can be produced by - ester of chlorformic acid or by pivaloyl chloride (Methoden der Organischen Chemie (Houben-Weyl) Band XV/2 Synthese von Peptiden, Georg Thieme Verlag, Stuttgart, 1974).

The coupling reaction can favourably be carried out in organic solvent preferably (at a temperature between - 25°C and the boiling point of the reaction mixture). Use of acid binding agents e.g. organic amines is favourable during the reaction.

The compounds of the general formula (I), can be purified, if appropriate, by a conventional purification technique, the isomers of which are separated, if desired, by a conventional separation technique and which are converted, if necessary, to their addition salts with a pharmaceutically acceptable acid.

Pharmaceutically acceptable acids may be for example hydrochloric, sulfuric, tartaric, fumaric methansulfonic acid and the like.

Another subject of the present invention is pharmaceutical compositions containing, as active principle, at least one compound of general formula (I) or one of its addition salts with a pharmacologically acceptable acid, alone or in combination with one or more inert and nontoxic excipients or vehicles.

Mention may more particularly be made, among pharmaceutical compositions according to the invention, of those which are suitable for oral, parenteral rectal or nasal administration, simple or sugar-coated tablets, sublingual tablets, injectable compositions, infusions, packets, gelatin capsules, suppositories, creams, ointments, dermal gels, and the like.

The dose varies according to the age and weight of the patient, the nature and the severity of the ailment and on the administration route.

The latter can be oral, nasal, rectal or parenteral. The unit dose generally varies between 0,1 and 50 mg/body weight kg for a treatment taken 1 to 3 times per 24 hours.

The invention will be further clarified by the following, tabular, non-limiting examples in greater detail and by a detailed process description in case of the example 4. Other embodiments of the invention will be apparent to the person skilled in the art from a consideration of this specification or practice of the invention disclosed herein.

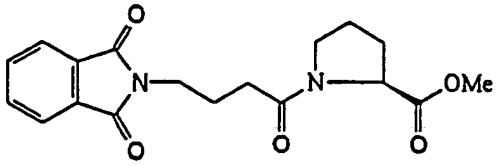
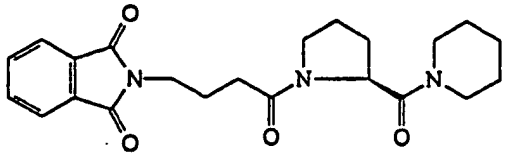
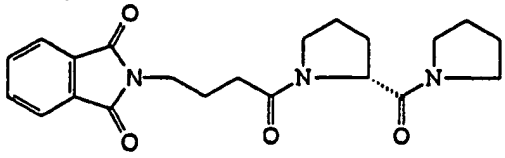
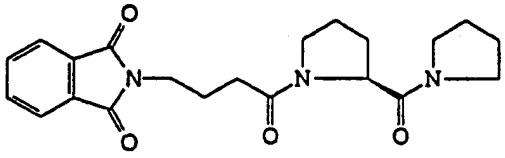
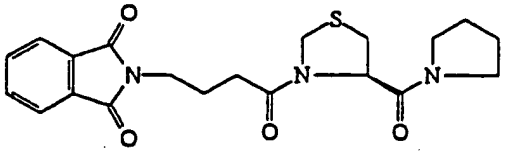
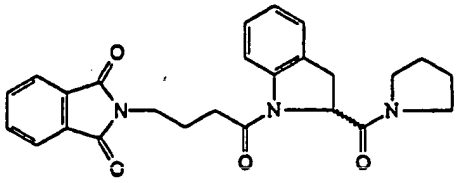
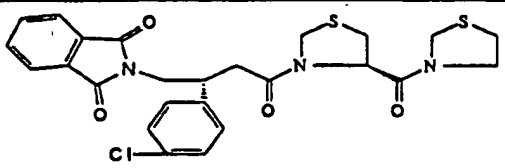
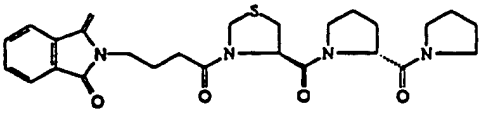
Examples

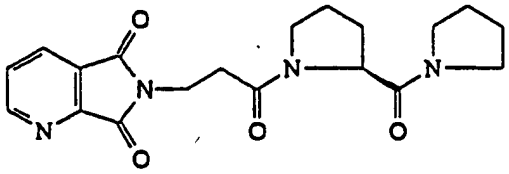
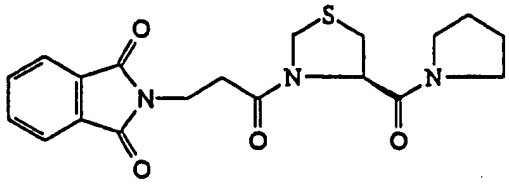
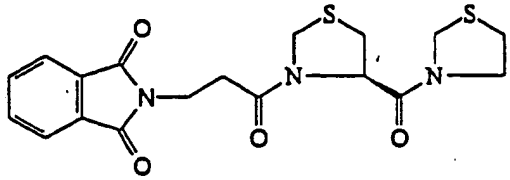
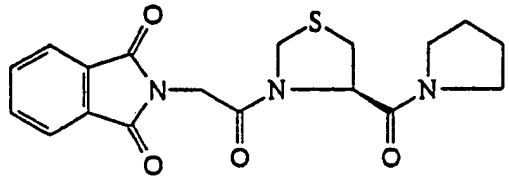
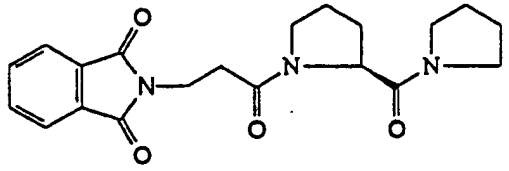
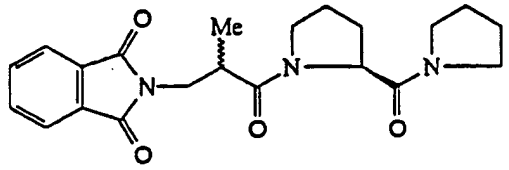
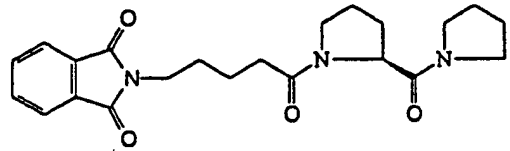
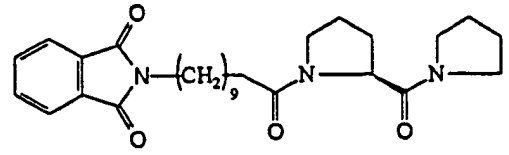
Description of the preparation of compound depicted in Example 4 (Table 1)

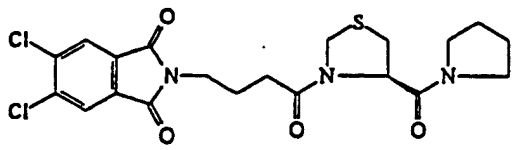
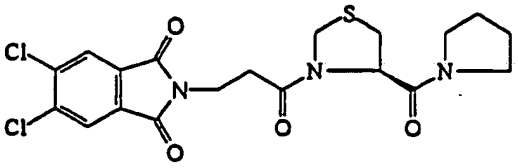
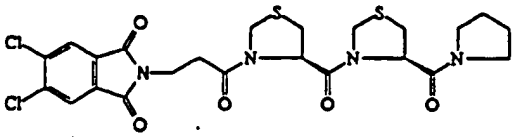
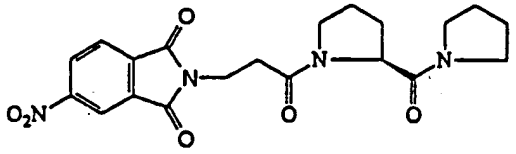
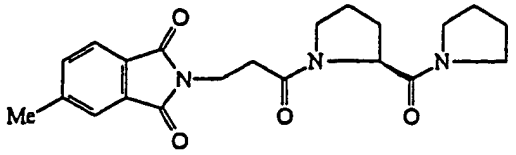
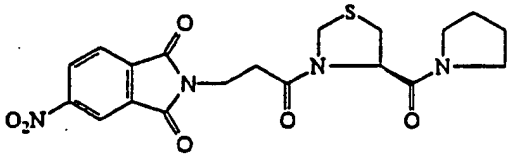
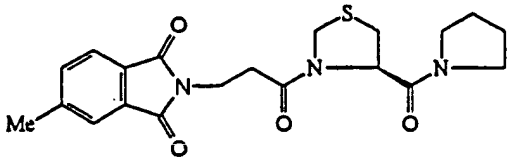
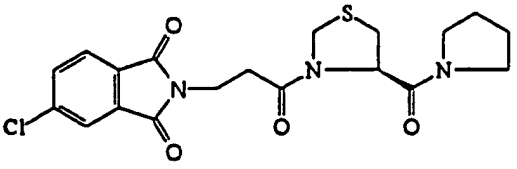
To a solution prepared by dissolving 1,17 g (5,0 mM) 4-phtalimido-butyric acid and 0,56 g (5,5 mM) triethylamin in 20 ml chloroform 0,61 g (5,0 mm) pivaloylchlorid were dropped at - 15 °C under stirring. The reaction mixture was stirred for 1 hour at the above temperature and then a solution prepared by dissolving 1,03 g (5,0 mM) L-prolyl-pyrrolidin-hydrochloric acid salt in a mixture of 5 ml chloroform and 1,5 ml (1,1 g, 11,0 mM) triethylamine were dropwise added to it. Reaction mixture was stirred at room temperature for 4 hours, then it was washed successively with water, 30 % cc. citric acid solution, saturated aqueous sodium bicarbonate solution, water and with saturated sodium chloride solution. The organic phase was dried on calcinated magnesium sulfate and it was evaporated. Crystallisation of the residue from a mixture of 5 ml chloroform and 10 ml petrolether yielded 1,1 g (53 %) N-(4-phtalimido-butanoyl)-L-prolyl-pyrrolidin which melted at 148-149 °C. The compounds of the general formula I were synthetised by the method as explained above starting from the corresponding compounds having general Formulas (II) and (III).

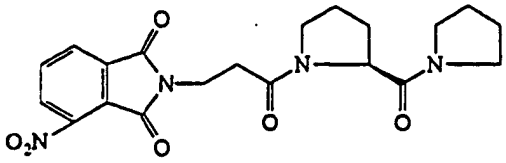
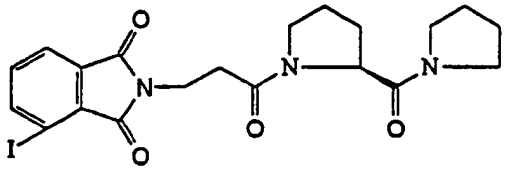
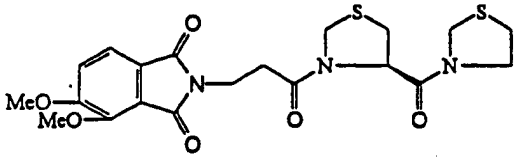
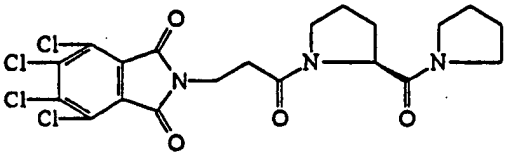
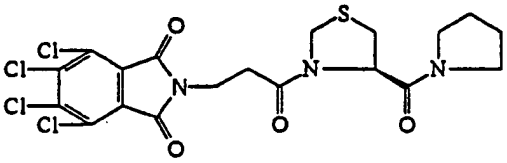
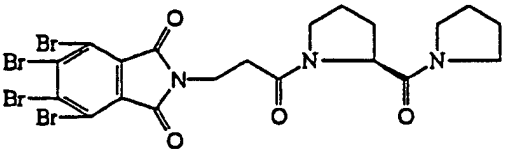
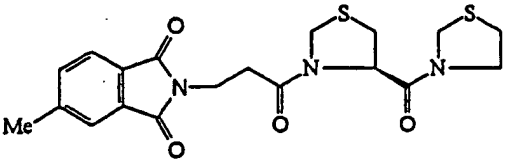
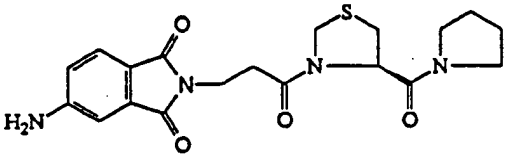
Structures and the physical constants of several novel compounds of the general Formula (I) are listed in Table 1.

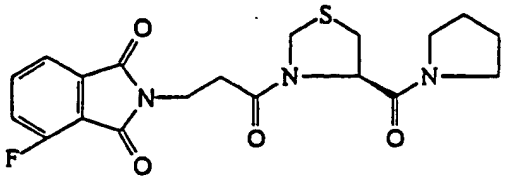
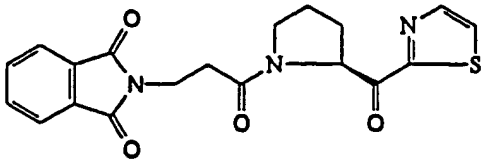
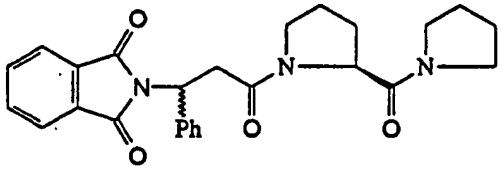
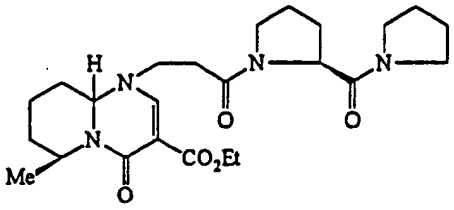
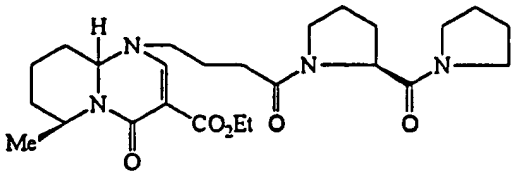
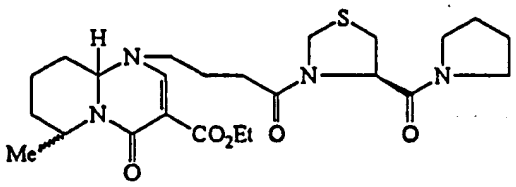
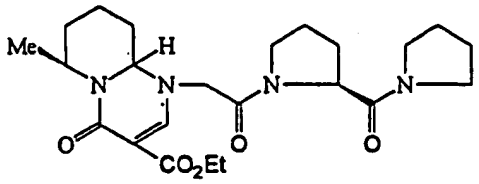
Table 1

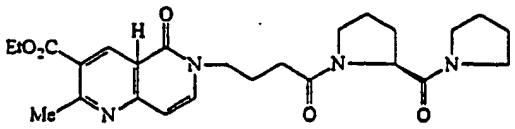
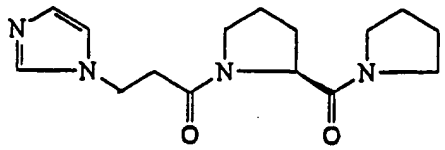
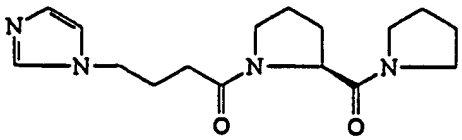
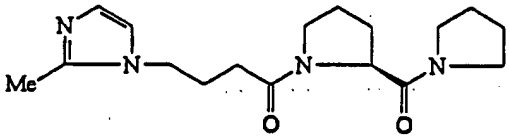
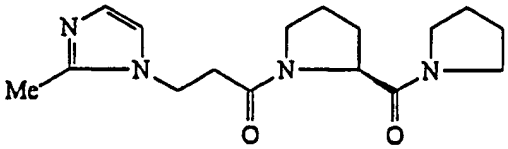
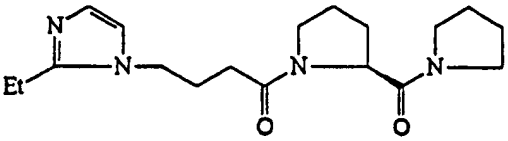
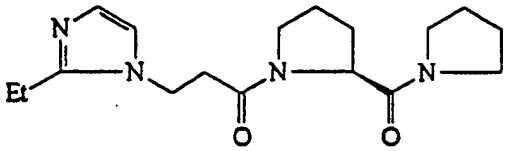
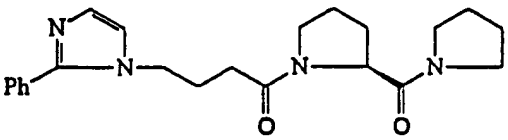
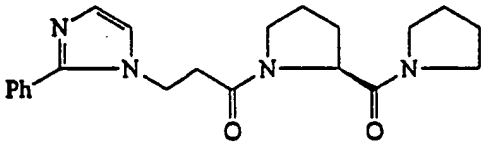
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
1		99-100	
2		oil	0.31[A]
3		146-147	
4		148-149	
5		oil	0.28[A]
6		131-132	
7		206-207	
8		oil	0.39[A]

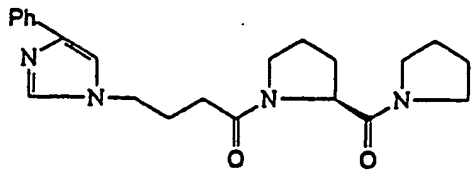
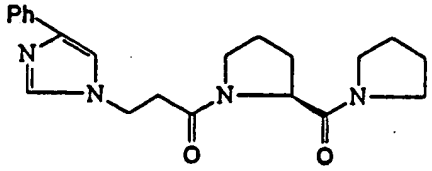
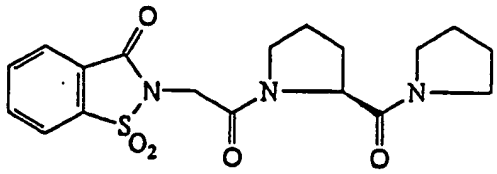
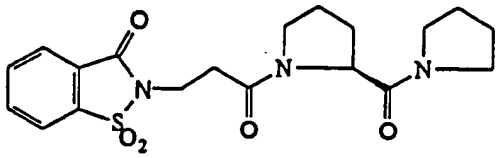
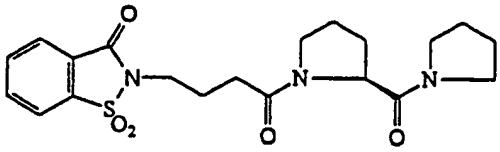
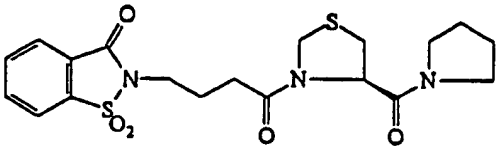
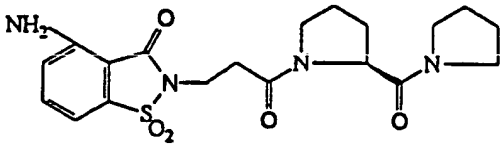
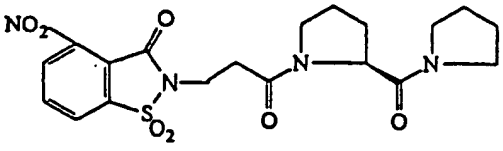
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
9		109-110	
10		168-169	
11		amorphous	0.38[A]
12		186-187	
13		oil	0.24[A]
14		oil	0.27[A]
15		oil	0.21[A]
16		oil	0.22[A]

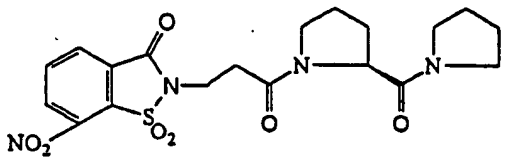
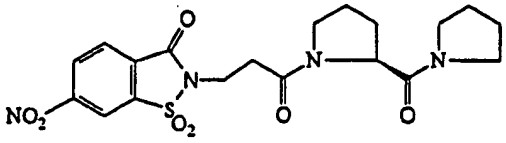
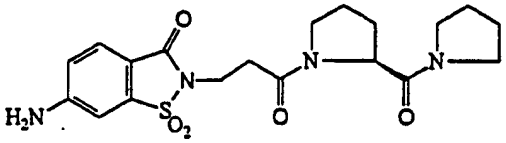
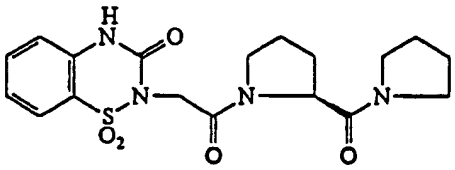
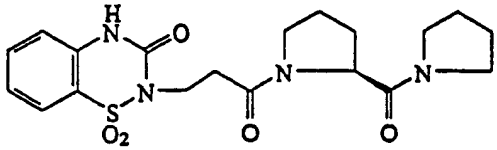
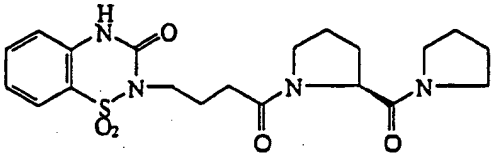
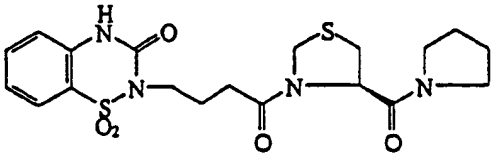
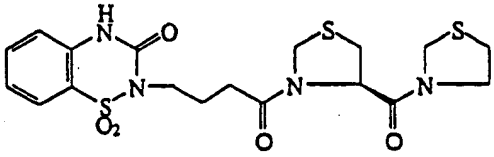
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
17		oil	0.44[A]
18		183-184	
19		207-208	
20		56- 62	
21		138-140	
22		169-171	
23		136-137	
24		130-131	

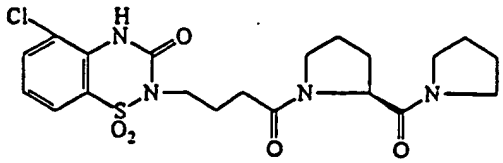
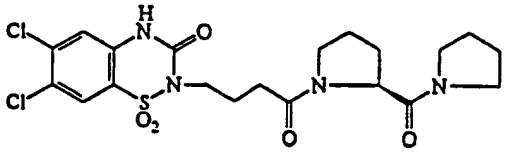
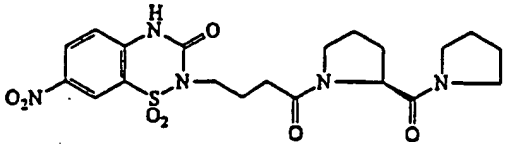
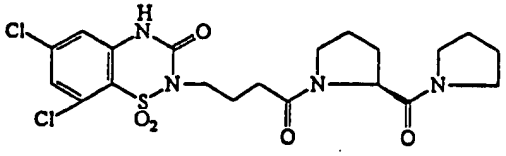
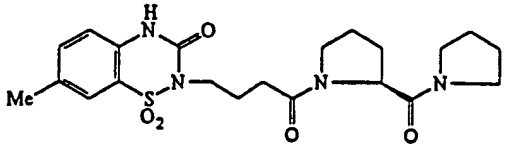
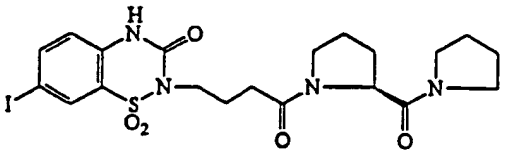
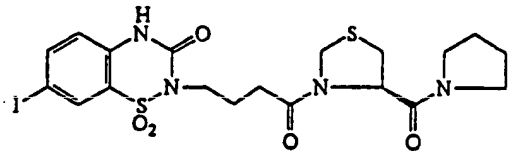
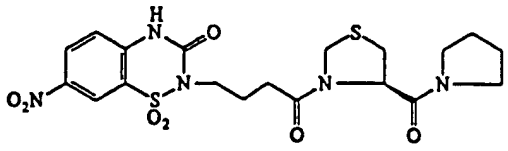
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
25		oil	0.32[A]
26		oil	0.41[A]
27		77- 79	
28		220-222	
29		224-225	
30		245-248	
31		133-134	
32		220-222	

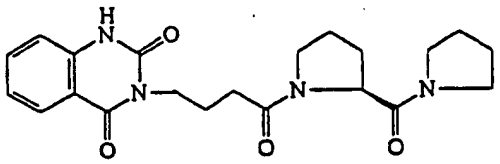
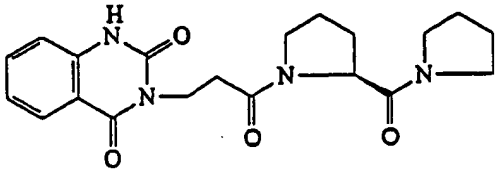
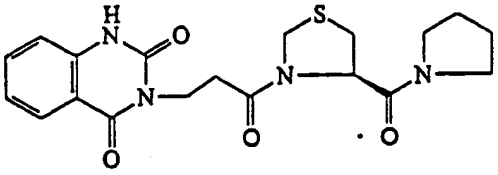
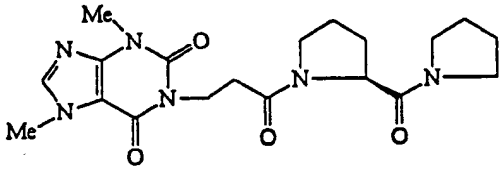
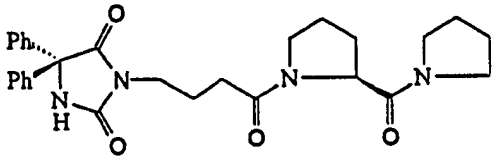
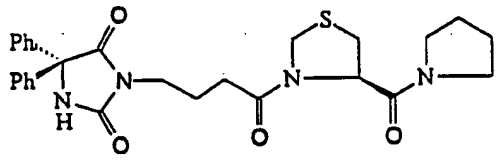
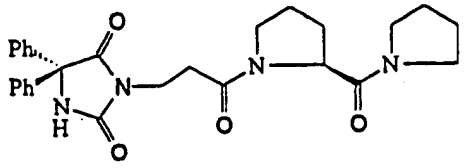
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
33		169-170	
34		138-139	
35		oil	0.35[A]
36		68- 70	
37		107-109	
38		amorphous	0.55[B]
39		105-112	

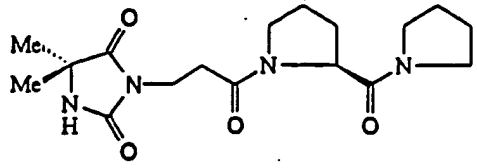
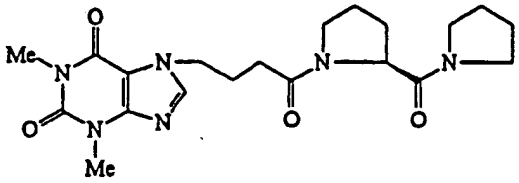
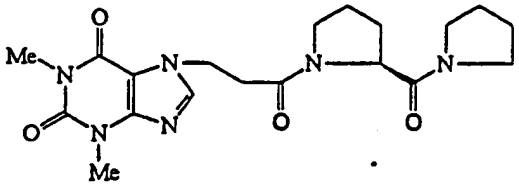
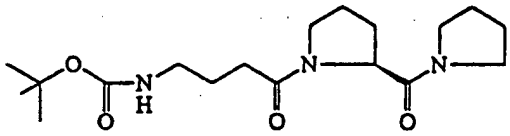
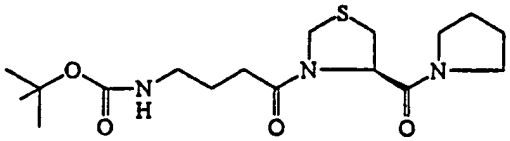
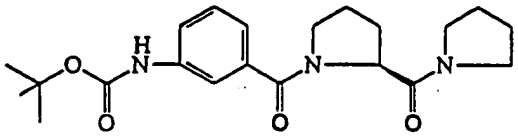
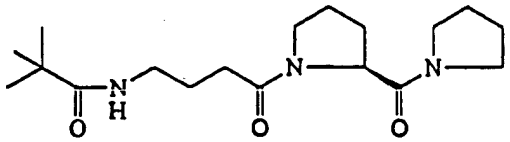
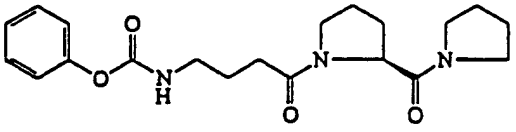
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
40		116-118	
41		oil	0.63[C]
42		oil	0.22[D]
43		oil	.036[C]
44		oil	0.50[C]
45		oil	0.72[C]
46		83- 86	
47		oil	0.72[F]
48		oil	0.70[F]

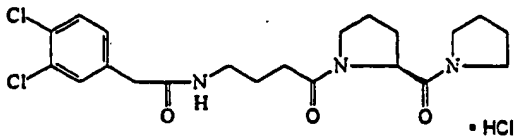
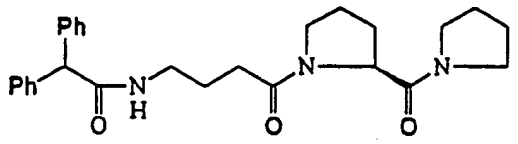
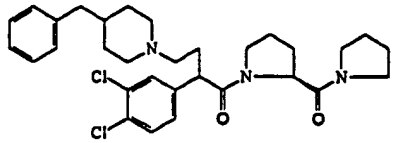
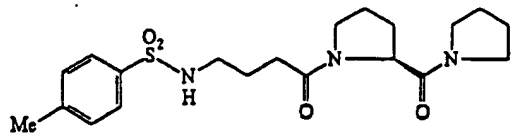
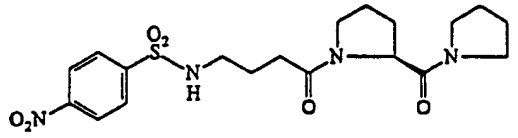
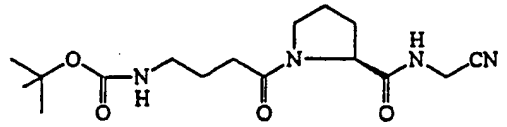
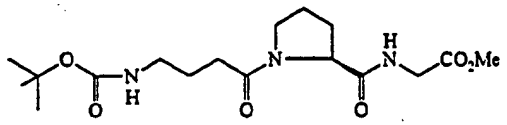
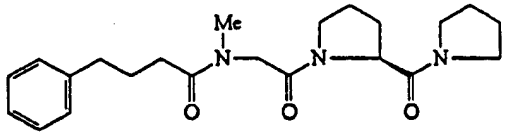
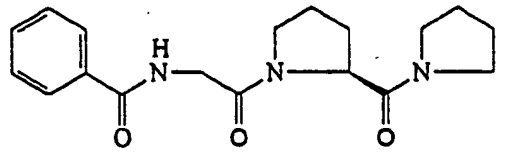
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
49		55- 60	
50		60- 62	
51		200-205	
52		85- 90	
53		122	
54		107-110	
55		185-190	
56		87	

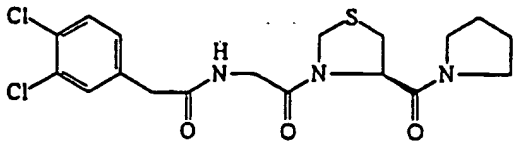
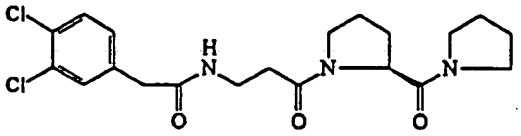
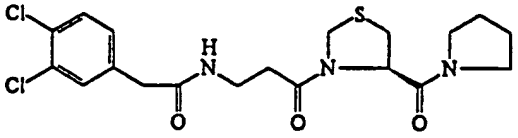
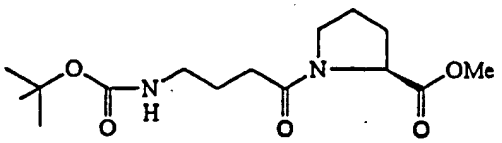
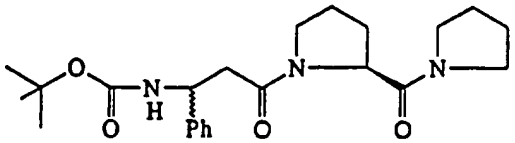
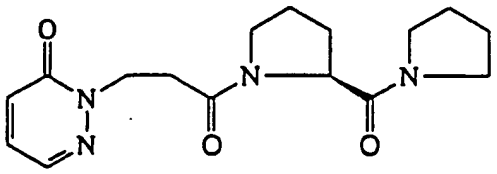
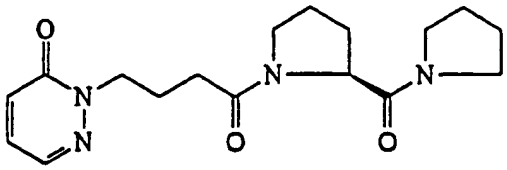
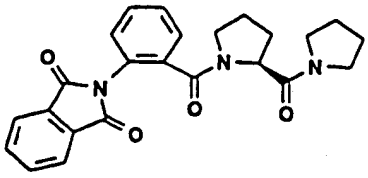
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
57		147	
58		95-100	
59		250	
60		155-157	
61		245	
62		60	
63		116	
64		85	

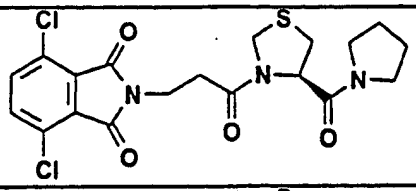
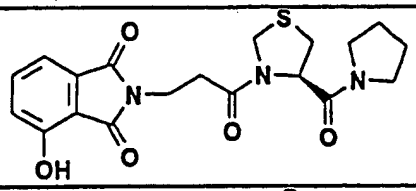
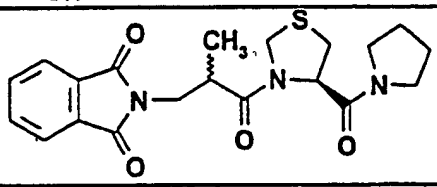
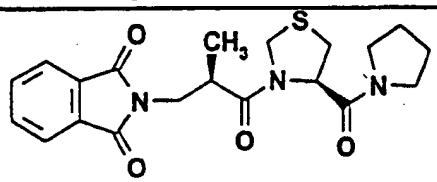
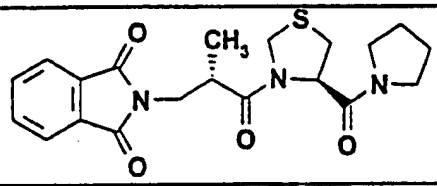
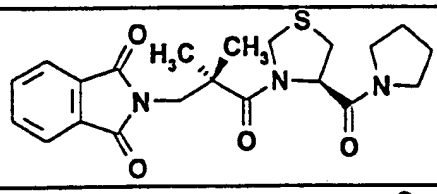
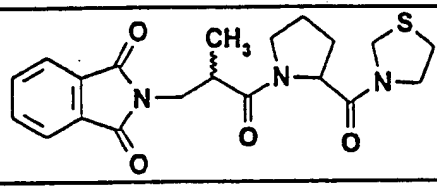
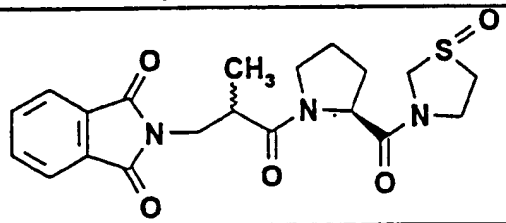
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
65		85	
66		194	
67		95	
68		225-226	
69		120	
70		138	
71		117	
72		113-118	

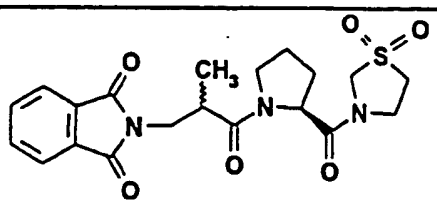
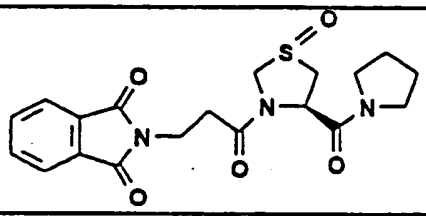
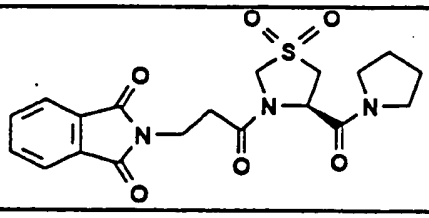
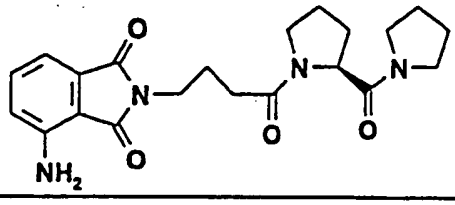
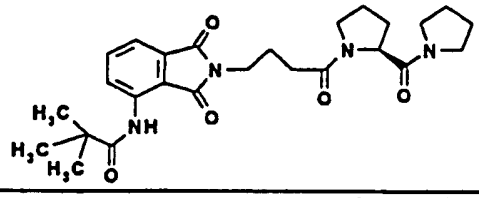
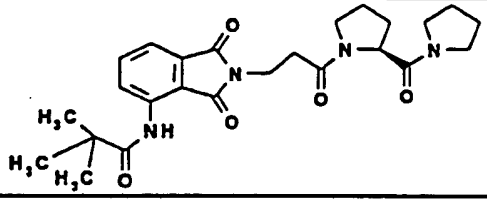
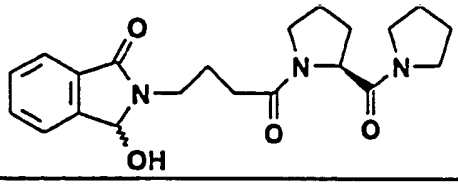
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
73		oil	0.70[D]
74		199-202	
75		197-198	
76		122-124	
77		230-232	
78		95- 97	
79		127-129	

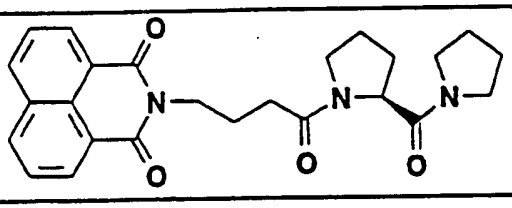
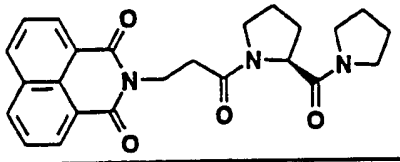
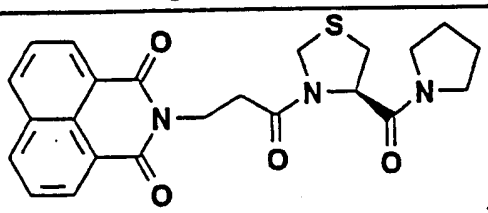
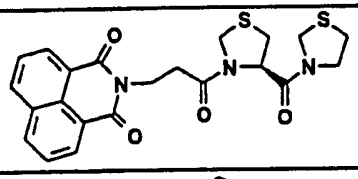
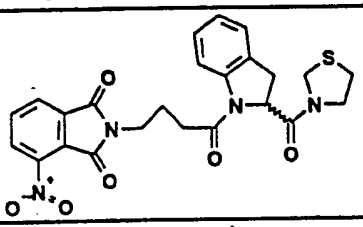
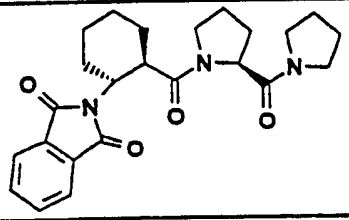
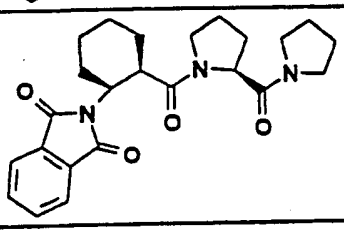
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
80		172-173	
81		204-205	
82		195-196	
83		oil	0.20[A]
84		139-140	
85		oil	0.19[A]
86		oil	0.25[A]
87		oil	0.40[B]

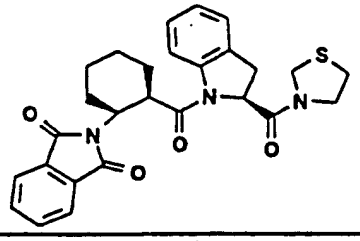
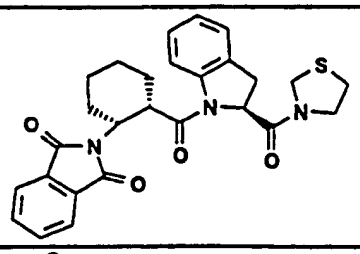
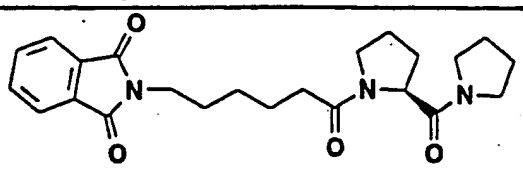
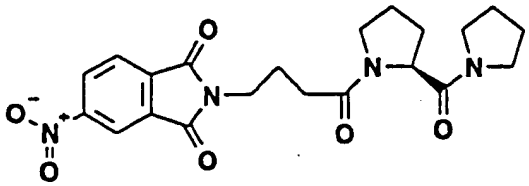
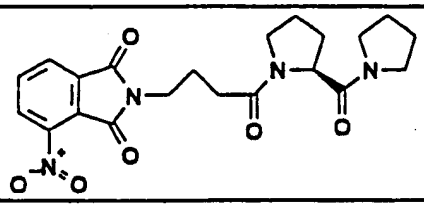
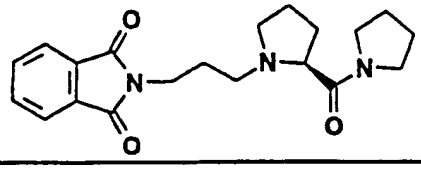
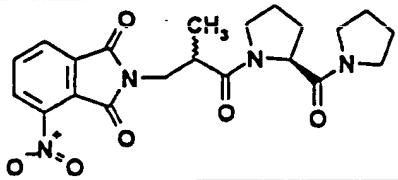
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
88		oil	0.45[B]
89		oil	0.45[B]
90		oil	0.50[B]
91		oil	0.10[A]
92		62- 66	
93		oil	0.40[E]
94		oil	0.45[E]
95		oil	0.34[A]
96		158-160	

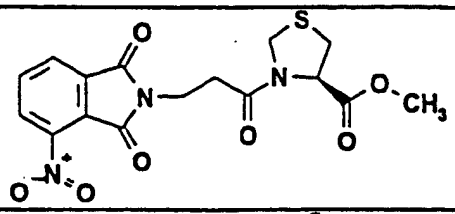
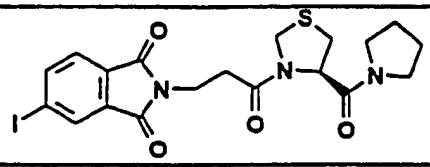
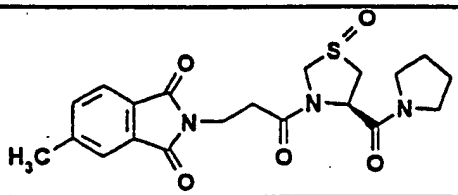
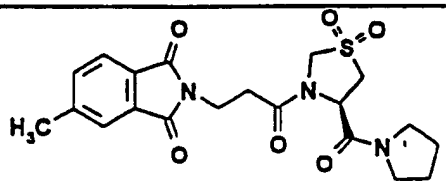
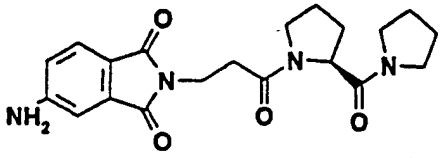
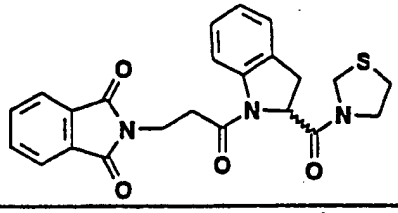
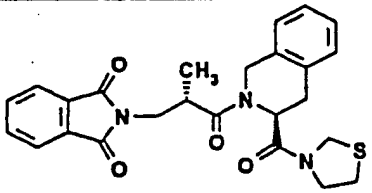
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
97		163-164	
98		oil	0.50[B]
99		oil	0.55[B]
100		oil	0.55[E]
101		oil	0.24[A]
102		oil	0.55[F]
103		oil	0.60[F]
104		70-74	

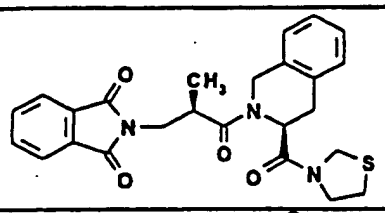
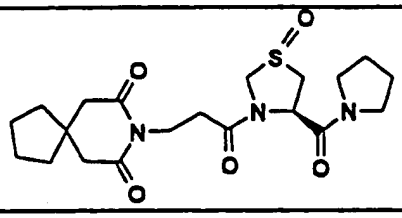
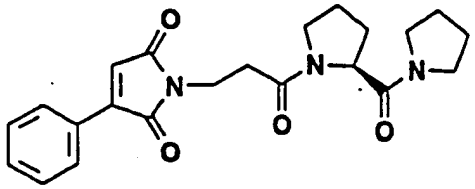
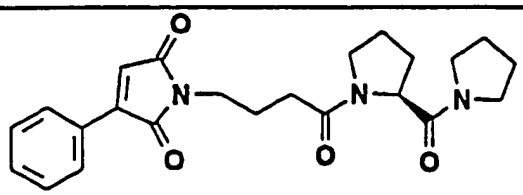
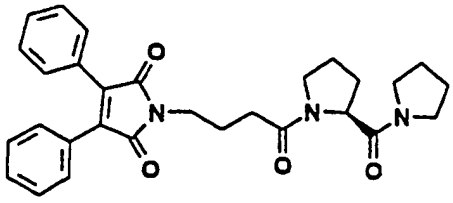
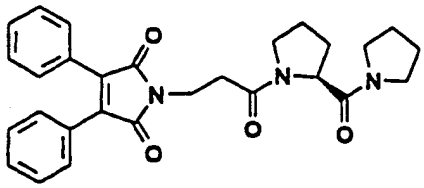
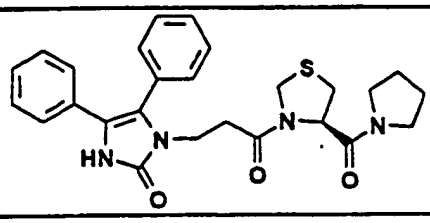
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
105		188-189	
106		164-165	
107		amorphous	075[A]
108[a]		amorphous	0.26[L]
109[a]		142-143	0.18[L]
110		163-164	
111		amorphous	0.34[A]
112		amorphous	0.24[A]

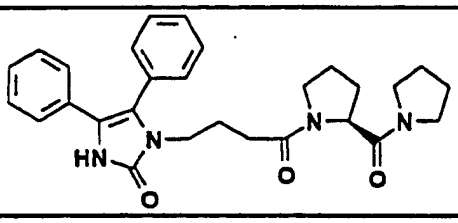
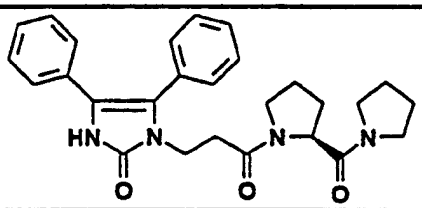
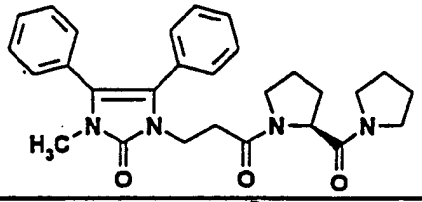
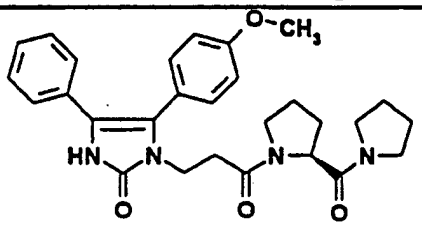
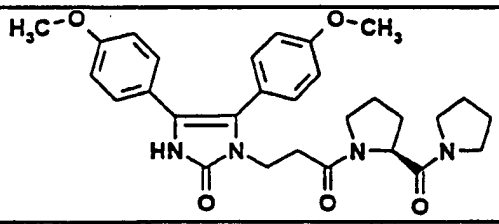
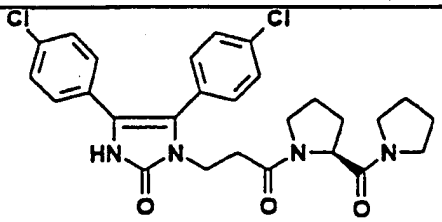
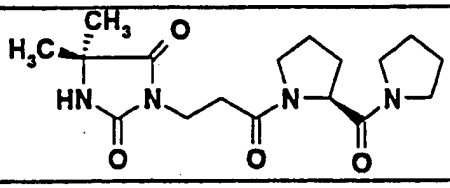
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
113		96-97	
114		74-75	
115		120-123	
116		195-197	
117		oil	0.35[A]
118		oil	0.29[A]
119		oil	0.22[A]

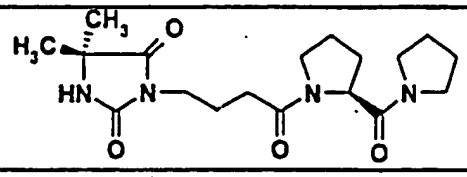
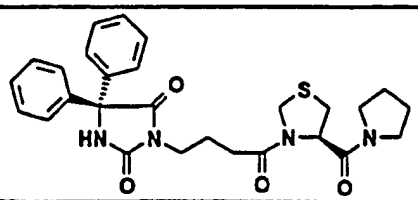
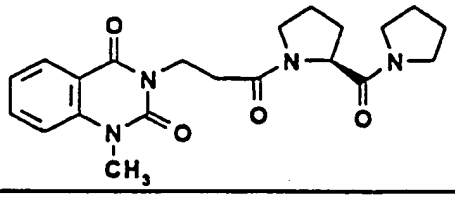
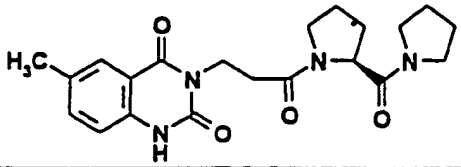
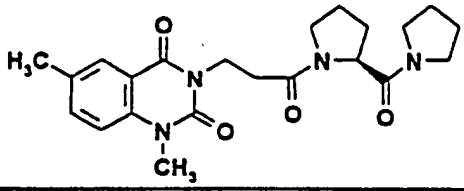
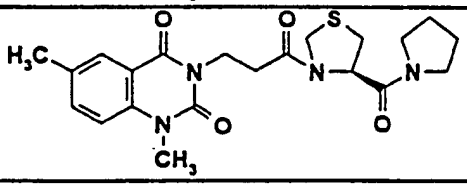
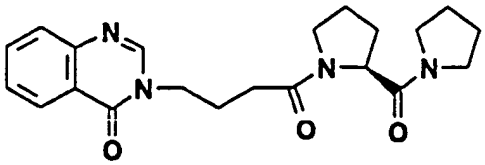
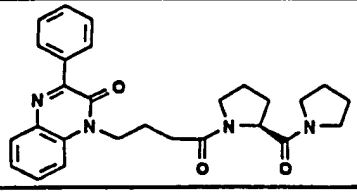
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
120		58-60	
121		168-169	
122		105-109	
123		173-175	
124		gradual melting	0.32[A]
125[b]		188-189	
126[b]		gradual melting	0.42[A]

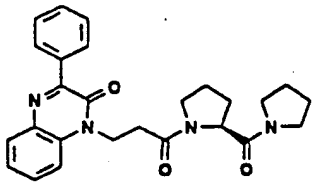
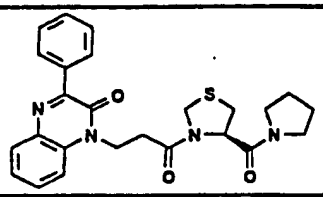
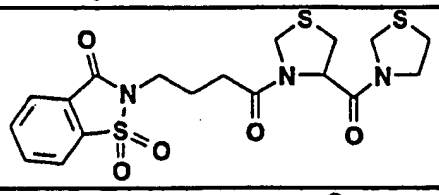
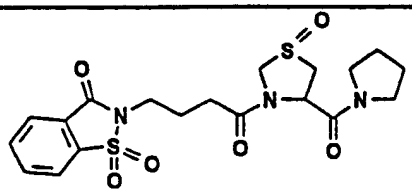
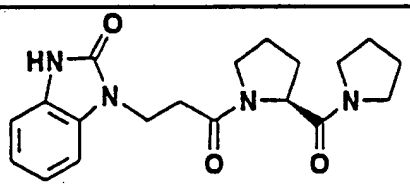
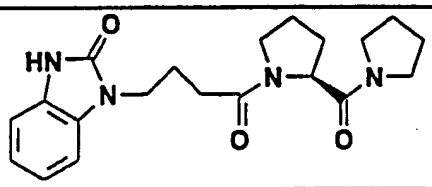
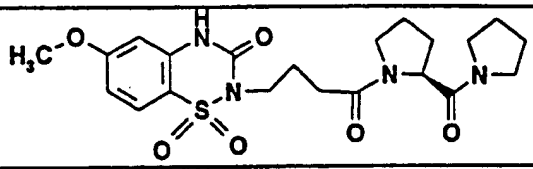
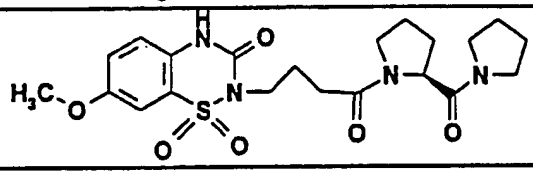
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
127[c]		127-131	
128[c]		181-183	
129		oil	0.41[A]
130		47-49	
131		amorphous	0.29[A]
132		oil	0.28[A]
133		amorphous	0.29[A]

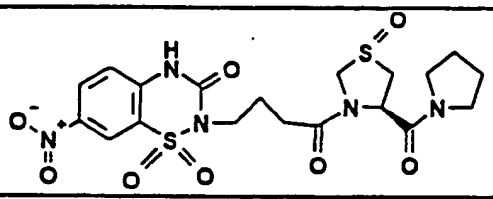
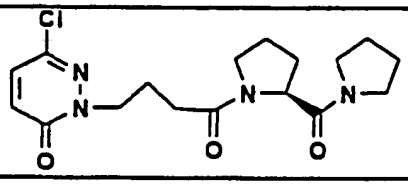
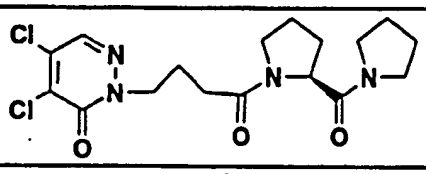
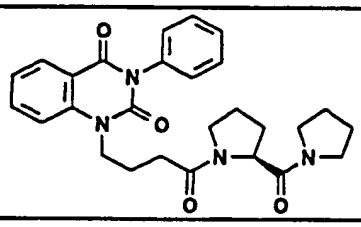
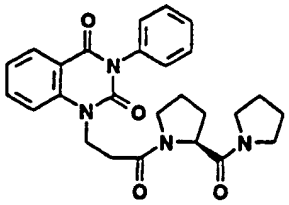
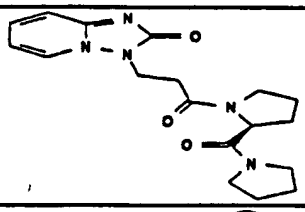
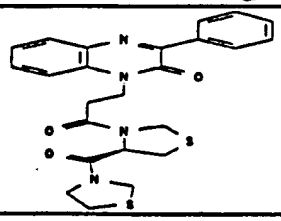
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
134		52	
135		166-168	
136		84-85	
137		103-105	
138		241-242	
139		>200	
140[d]		78-79	0.41[K]

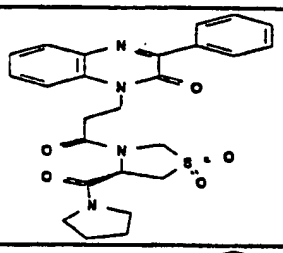
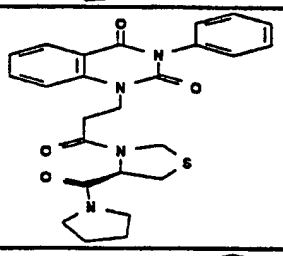
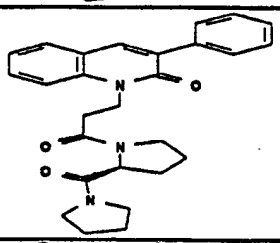
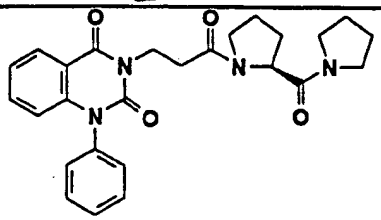
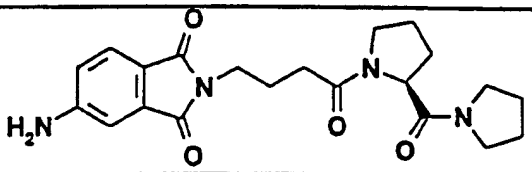
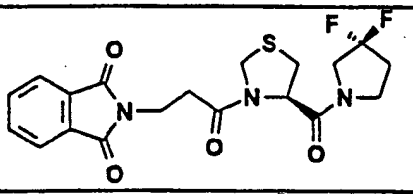
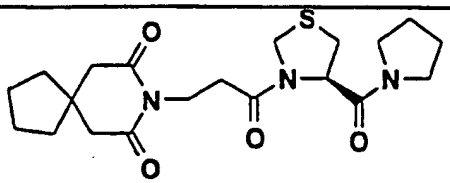
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
141[d]		78-79	0.29[K]
142		173-174	
143		68-72	
144		80-82	
145		72-75	
146		160-165	
147		260-262	

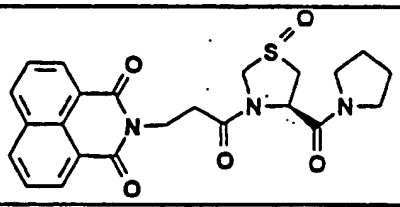
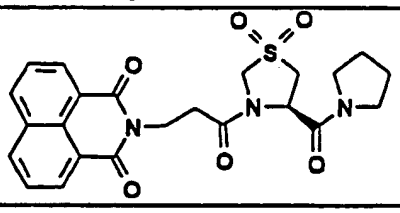
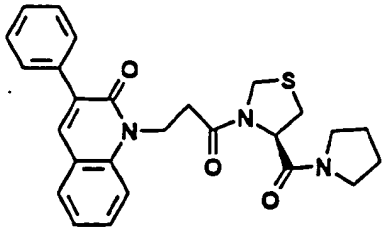
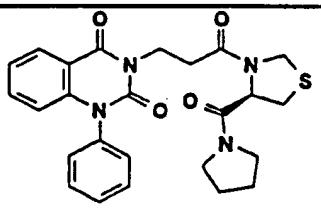
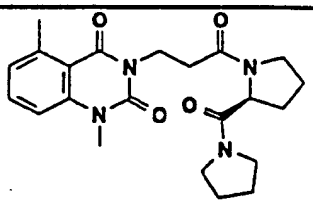
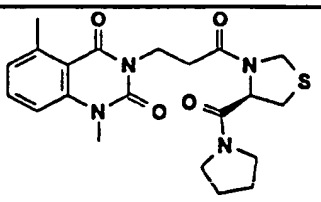
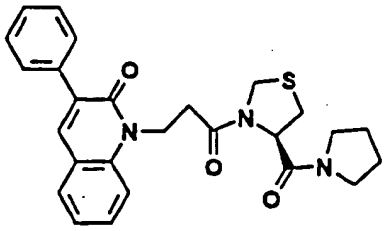
No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
148		140-145	
149		268-270	
150		208-211	
151		236-240	
152		245-250	
153		274-280	
154		172-173	

No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
155		173	
156		95-97	
157		105-107	
158		137-139	
159		201-203	
160		167-169	
161		78	
162		159-160	

No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
163		221-226	
164		246-248	
165		95	
166		55-59	
167		99	
168		65	
169		110	
170		78	

No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
171		181-184	
172		oil	0.52[F]
173		114-115	0.66[F]
174		94-96	
175		158-160	
176		95-100	
177		217-222	

No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
178		144	
179		174-178	
180		95-105	
181		132-135	
182		237-238	
183		137-138	
184		148-150	

No. of examples	Structural formula of compounds	Melting point (°C)	Retention factor
185			0.26[A]
186		191-192	
187		176-180	
188		143-145	
189		178-180	
190		181-183	
191		95-105	

[a, b, c, d] tentative assignment of epimers, maybe reverse

Abbreviations of eluents:

A CM201 Chloroform: methanol = 20: 1

B BM 41 Benzene methanol = 4: 1

C CM 41 Chloroform methanol = 4: 1

D DM101 Dichloromethane methanol = 10: 1

E CM955 Chloroform methanol = 95: 5

F CM 91 Chloroform methanol = 9: 1

G DM 91 Dichlormethane methanol = 9: 1

I HA 21 n-Hexane acetone = 2: 1

J HA 31 n-Hexane acetone = 3: 1

K CA 101 Chloroform acetone = 10: 1

Claims

1.) Compounds of the general formula (I) wherein A means an onefold of manifold substituted or unsubstituted organic cyclic group containing one nitrogen atom with one free valency and optionally one or more further heteroatom selected from a group consisting of nitrogen atom, sulfuratom or oxigenatom, especially groupg having the general formula (1), (1a), (2), (2a), (3), (3a), (4), (5), (6), (7), (8), (9), (10), (11a), (11b), (12), (12a), (12b), (13), (13a), (14), (15), (16), (17), (18), (19), (19a), (20), (20a), (21), (22), (23), (23a), (23b), (24), (25), (25a), (26), (27), (28), (28a), (28b), (29), (29a), (30), (31), (32), (32a), (33), (34), (35), (36) - wherein

R means hydrogenatom alkyl group of 1-4 carbon atoms or aryl or aralkyl group of 6-12 carbon atoms;

R^1, R^2, R^3 and R^4 mean independently from each other hydrogen atom, halogen atom, hydroxyl group, straight chain or branched chain alkyl or alkenyl- or alkinyl or alkoxy- or alkenyloxy- or alkinyloxy groups containing 1-6 carbon atoms, nitro-group, amino group, monoalkylamino or monoacylamino group of 1-12 carbon atoms ,dialkylamino- or diacylamino group of 2-24 carbon atoms - where the acyl group is an alkyl, aralkyl, cycloalkyl or aryl type -, cyano group, mercapto group, carboxyl group, esterified carboxyl group of 2-7 carbon atoms, hydroxyalkyl group of 1-6 carbon atoms, acyl group of 1-7 carbon atoms, acyloxy group of 1-7 carbon atoms, phenyl or benzyl group, anilino group, benzoyl group, phenoxy group, benzyloxy group, isocyanato group, isothiocyanato group, alkylthio group of 1-6 carbon atoms, sulfamino or sulfamoyl group, thiocyanato or cyanato group;

R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group phenyl group or alkyl group of 1- 4 carbon atoms or R^5 and R^6 together mean oxo group;

R^7 means alkyl group of 1-6 carbon atoms;

R^8 means hydrogen atom or alkyl group of 1-6 carbon atoms or aralkyl group of 7-10 carbon atoms;

the dotted line means an optional chemical bond;

n is zero 1, 2 or 3;

X means-CH_2-group, -NH-group, carbon atom, hydrogen atom, oxygen atom or amino group; or

A means an R' - Y - N = group or R'-Y-N(R^9)- group - wherein R' means alkyl group of 1-6 carbon atoms, aralkyl group of 7-10 carbon atoms, diphenylmethyl group, alkoxy group , arylalkyloxy group of 7-10 carbon atoms, or phenyl- or phenoxy or phenylalkyl group containing 7-10 carbon atoms or phenylalkyloxy group containing 7-10 carbon atoms optionally substituted with halogen atoms or alkyl groups of 1-4 carbon atoms or nitro groups; Y means chemical bond or oxo-, sulfonyl- or sulfinyl group, R^9 means hydrogen atom or alkyl group of 1-4 carbon atoms; - with the proviso that in the case of formulas (20) and (33) X cannot mean - CH_2- group, - NH- group, oxygen atom or sulfur atom and in the case of formulas (30) and (31) X cannot mean - CH_2- group, oxygen atom or sulfur atom or amino group;

B means $-(CH_2)_m-\overset{O}{\overset{\|}{C}}-$ group - wherein m is an integer of 1 to 21; or

$-O-(CH_2)_p-\overset{O}{\overset{\|}{C}}-$ group wherein p is an integer of 1 to 3; or

$-\overset{R^9}{\overset{|}{C}}-\left[\overset{R^{13}}{\overset{|}{C}}\right]_w-\overset{R^{14}}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}-$ group - wherein R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean independently from each other hydrogen alkyl or alkoxy group of 1-6 carbonatoms, halogen, amino group optionally substituted with one or two alkyl group of 1-6 carbonatoms; or

phenyl, phenoxy, aryl-alkyl group of 7-12 carbonatoms or aryl-alkoxy group of 7-12 carbonatoms each of them optionally containing 1, 2 or 3 same or different substituents identical to R^1, R^2, R^3 or R^4; or

two of R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean together an oxo or epoxy group or further chemical bond or four of them mean together two further chemical bonds and the remaining groups stand for hydrogen atoms; or

R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean together with the chain carbonatoms a saturated or unsaturated homocycle containing 3-8 carbon atoms or a saturated or unsaturated heterocycle containing 2-7 carbon atoms and a nitrogen or sulfur or oxygen atom, to which optionally an aromatic ring of 6-10 carbon atoms is condensed; and

w is zero or 1;

C means prolyl group or one of the groups of formula (37), (38), (39), (40) or (41) - where n is zero or 1 or 2, Hlg means fluorine, chlorine, bromine, or iodine atom;

R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group phenyl group or alkyl group of 1-4 carbonatoms or R^5 and R^6 together mean oxo-group;

R^{16} means an alkoxy group of 1-4 carbon atoms, or -NH- CH_2 -CN group. or - NH-CH_2-CO_2R^7 group - where R^7 is defined as above; or

D or L structural unit; or one of the group of the formula (42) or (43) or (43a) - where the dotted line means a chemical bond optionally present-, s is 1, 2 or 3 - or a group of the formula (44) -wherein R^{15} means hydrogen atom, alkyl group of 1-6 carbon atoms, phenyl or naphthyl group; or

a group of the formula (45) - wherein Z means NH - group, oxygen atom or sulfur atom;

D means a covalent chemical bond or prolyl- or thioprolyl group, or one of groups of formula (37) or (38), (39), (40) or (41);

L means pyrrolidino- or 2- cyanopyrrolidino, thiazolidino or 2-cyano-thiazolidino or piperidino group optionally substituted with one halogen atom or geminally with two halogen atoms; or

a group of the formula (46) - where R^{17} means hydrogen atom or cyano group, n is 0, 1 or 2 ; or

a group of the formula (47) or (48) or (49); -

and optical , cis-trans, geometric isomers , epimers, tautomers, salts, prodrugs and human and mammalian metabolites of them.

2.) Compounds of the general formula (I),- wherein A means one of the groups having general formula (1), (1a), (2), (2a), (3), (3a), (4), (5), (6), (7), (8), (9), (10), (11a), (11b), (12), (12a), (12b), (13), (13a), (14), (15), (16), (17), (18), (19), (19a), (20), (20a), (21), (22), (23), (23a), (23b), (24), (25), (25a), (26), (27), (28), (28a), (28b), (29), (29a), (30), (31), (32), (32a), (33), (34), (35), (36) - wherein

R means hydrogenatom alkyl group of 1-4 carbon atoms or aryl or aralkyl group of 6-12 carbon atoms,

R^1, R^2, R^3 and R^4 mean independently from each other hydrogen atom, halogen atom, hydroxyl group, straight chain or branched chain alkyl or alkenyl- or alkinyl or alkoxy- or alkenyloxy- or alkinyloxy groups containing 1-6 carbon atoms, nitro-group, amino group, monoalkylamino or monoacylamino group of 1-12 carbon atoms ,dialkylamino- or diacylamino group of 2-24 carbon atoms - where the acyl group is an alkyl, aralkyl, cycloalkyl or aryl type -, cyano group, mercapto group,

carboxyl group, esterified carboxyl group of 2-7 carbon atoms, hydroxyalkyl group of 1-6 carbon atoms, acyl group of 1-7 carbon atoms, acyloxy group of 1-7 carbon atoms, phenyl or benzyl group, anilino group, benzoyl group, phenoxy group, benzyloxy group, isocyanato group, isothiocyanato group, alkylthio group of 1-6 carbon atoms, sulfamino or sulfamoyl group, thiocyanato or cyanato group;

R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group, phenyl group or alkyl group of 1- 4 carbon atoms or R^5 and R^6 together mean oxo group;

R^7 means alkyl group of 1-6 carbon atoms;

R^8 means hydrogen atom or alkyl group of 1-6 carbon atoms or aralkyl group of 7-10 carbon atoms;

the dotted line means an optional chemical bond;

n is zero, 1, 2 or 3;

X means $-CH_2-$group, -NH-group, carbon atom, hydrogen atom, oxygen atom or amino group; or

A means an R` - Y - N = group or R`-Y-$\underset{\displaystyle R^9}{\underset{|}{N}}$- group - wherein R` means alkyl group of 1-6 carbon atoms, aralkyl group of 7-10 carbon atoms, diphenylmethyl group, alkoxy group , arylalkyloxy group of 7-10 carbon atoms, or phenyl- or phenoxy or phenylalkyl group containing 7-10 carbon atoms or phenylalkyloxy group containing 7-10 carbon atoms optionally substituted with halogen atoms or alkyl groups of 1-4 carbon atoms or nitro groups; Y means chemical bond or oxo-, sulfonyl- or sulfinyl group, R^9 means hydrogen atom or alkyl group of 1-4 carbon atoms; - with the proviso that in the case of formulas (20) and (33) X cannot mean - CH_2- group, -NH- group, oxygen atom or sulfur atom and in the case of formulas (30) and (31) X cannot mean - CH_2- group, oxygen atom or sulfur atom or amino group;

B means $-(CH_2)_m-\underset{\displaystyle O}{\underset{\|}{C}}-$ group - wherein m is an integer of 1 to 21; or

$-O-(CH_2)_p-\underset{\displaystyle O}{\underset{\|}{C}}-$ group wherein p is an integer of 1 to 3; or

$-\underset{\displaystyle R^9}{\underset{|}{C}}-\left[\underset{\displaystyle R^{10}}{\underset{|}{C}}\right]_w-\underset{\displaystyle R^{11}}{\underset{|}{C}}-\underset{\displaystyle O}{\underset{\|}{C}}-$ group - wherein R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean independently from each other hydrogen alkyl or alkoxy group of 1-6 carbonatoms, halogen, amino group optionally substituted with one or two alkyl group of 1-6

carbonatoms; or

phenyl, phenoxy, aryl-alkyl group of 7-12 carbonatoms or aryl-alkoxy group of 7-12 carbonatoms each of them optionally containing 1, 2 or 3 same or different substituents identical to R^1, R^2, R^3 or R^4; or

two of R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean together an oxo or epoxy group or further chemical bond or four of them mean together two further chemical bonds and the remaining groups stand for hydrogen atoms; or

R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean together with the chain carbonatoms a saturated or unsaturated homocycle containing 3-8 carbon atoms or a saturated or unsaturated heterocycle containing 2-7 carbon atoms and a nitrogen or sulfur or oxygen atom, to which optionally an aromatic ring of 6-10 carbon atoms is condensed; and

w is zero or 1;

C means prolyl group or one of the groups of formula (37), (38), (39), (40) or (41) - where n is zero or 1 or 2, Hlg means fluorine, chlorine, bromine, or iodine atom; R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group phenyl group or alkyl group of 1-4 carbonatoms or R^5 and R^6 together mean oxo-group;

R^{16} means an alkoxy group of 1-4 carbon atoms, or -NH- CH_2 -CN group, or -NH-CH_2-CO_2R^7 group - where R^7 is defined as above; or

D or L structural unit; or one of the group of the formula (42) or (43) or (43a) - where the dotted line means a chemical bond optionally present-, s is 1, 2 or 3 or a group of the formula (44) -wherein R^{15} means hydrogen atom, alkyl group of 1-6 carbon atoms, phenyl or naphthyl group; or

a group of the formula (45) - wherein Z means NH - group, oxygen atom or sulfur atom;

D means a covalent chemical bond or prolyl or thioprolyl group, or one of groups of formula (37) or (38), (39), (40) or (41);

L means pyrrolidino- or 2- cyanopyrrolidino, thiazolidino or 2-cyano-thiazolidino or piperidino group optionally substituted with one halogen atom or geminally with two halogen atoms; or

a group of the formula (46) - where R^{17} means hydrogen atom or cyano group, n is 0, 1 or 2 ; or

a group of the formula (47) or (48) or (49); -

and optical , cis-trans, geometric isomers , epimers, tautomers, salts, prodrugs and human and mammalian metabolites of them.

3.) Compounds according to claim 2 - wherein A means a group of the general formula (2Oa) or (23a) - wherein R means hydrogenatom, alkyl group of 1-4 carbon atoms or aryl or aralkyl group of 6-12 carbon atoms,

R^1, R^2, R^3 and R^4 mean independently from each other hydrogen atom, halogen atom, hydroxyl group, straight chain or branched chain alkyl or alkenyl- or alkinyl or alkoxy- or alkenyloxy- or alkinyloxy groups containing 1-6 carbon atoms, nitro-group, amino group, monoalkylamino or monoacylamino group of 1-12 carbon atoms ,dialkylamino- or diacylamino group of 2-24 carbon atoms - where the acyl group is an alkyl, aralkyl, cycloalkyl or aryl type -, cyano group, mercapto group, carboxyl group, esterified carboxyl group of 2-7 carbon atoms, hydroxyalkyl group of 1-6 carbon atoms, acyl group of 1-7 carbon atoms, acyloxy group of 1-7 carbon atoms, phenyl or benzyl group, anilino group, benzoyl group, phenoxy group, benzyloxy group, isocyanato group, isothiocyanato group, alkylthio group of 1-6 carbon atoms, sulfamino or sulfamoyl group, thiocyanato or cyanato group;

R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group or phenyl group or alkyl group of 1- 4 carbon atoms or R^5 and R^6 together mean oxo group;

R^7 means alkyl group of 1-6 carbon atoms;

R^8 means hydrogen atom or alkyl group of 1-6 carbon atoms or aralkyl group of 7-10 carbon atoms;

the dotted line means an optional chemical bond;

X means-CH_2-group, -NH-group, carbon atom, hydrogen atom,
oxygen atom or amino group;

B means $-(CH_2)_m-\overset{\overset{O}{\|}}{C}-$group wherein m is 2 or 3;

C means a prolyl group or a group of the general formula (38) or (41) - wherein n is 1 or 2;

D means a covalent chemical bond;.

L means a pyrrolidino or thiazolidino group - and optical, cis-trans, geometric isomers, epimers, tautomers salt produgs and human and mammalian metabolites of them.

4.) Pharmaceutical composition containing one or more compounds of the general formula (I) - wherein the meanings of A, B, C, D, and L are as given in claim 1 and 2 - and/or optical, cis-trans, geometric isomers, epimers, tautomers, salts, prodrugs and human and mammalian metabolites of them, alone or together with usual carrier and/or auxiliary materials applied in the pharmaceutical industry.

5.) A process for the preparation of compounds of the general formula (I) - where in the meanings of A, B, C, D, and L are as given in claim 1 and 2 - and optical, cis-trans, geometric isomers, epimers, tautomers and their salts, characterized in that a racemic or optically active carboxylic acid of the general formula (II) - where the meanings of A and B are as given in claim 1 and 2 - is transformed to an acid halide, or an active ester, or to a mixed acid anhydride or to a carbodiimide, and the resulted compound is reacted with a racemic or optically active compound or their salt of the general formula (III), - where the meanings of C, D and L are as given in claim 1 - and the resulted compound of the general formula (I) - where the meanings of A, B, C, D, and L are as given in claim 1 and 2 - optionally is separated into the their optical, cis-trans, geometric isomers, epimers or tautomers or a salt of compounds of general formula (I) is formed, or the compounds of general formula (I) are liberated from their salts.

6.) Use of the compounds of the general formula (I) defined in claim 1 and 2 for inhibition of prolyl-endopeptidase enzyme in mammals including man.

7.) Compounds of the general formula (I),- wherein A means one of the groups having general formula (1), (2), (2a), (3), (3a), (4), (5), (6), (7), (8), (9), (10), (11a), (11b), (12), (12a), (13), (13a), (14), (15), (16), (17), (18), (19), (20), (21), (22), (23), (24), (25), (25a), (26), (27), (28), (28a), (29), (30), (31), (32), (32a), (33), (34), (35), (36) - wherein

R means hydrogenatom alkyl group of 1-4 carbon atoms or aryl or aralkyl group of 6-10 carbon atoms,

R^1, R^2, R^3 and R^4 mean independently from each other hydrogen atom, halogen atom, hydroxyl group, straight chain or branched chain alkyl or alkenyl- or alkinyl or alkoxy- or alkenyloxy- or alkinyloxy groups containing 1-6 carbon atoms, nitro-group, amino group, monoalkylamino or monoacylamino group of 1-12 carbon atoms ,dialkylamino- or diacylamino group of 2-24 carbon atoms - where the acyl

group is an alkyl, aralkyl, cycloalkyl or aryl type -, cyano group, mercapto group, carboxyl group, esterified carboxyl group of 2-7 carbon atoms, hydroxyalkyl group of 1-6 carbon atoms, acyl group of 1-7 carbon atoms, acyloxy group of 1-7 carbon atoms, phenyl or benzyl group, anilino group, benzoyl group, phenoxy group, benzyloxy group, isocyanato group, isothiocyanato group, alkylthio group of 1-6 carbon atoms, sulfamino or sulfamoyl group, thiocyanato or cyanato group;

R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group or phenyl group or alkyl group of 1- 4 carbon atoms or R^5 and R^6 together mean oxo group;

R^7 means alkyl group of 1-6 carbon atoms;

R^8 means hydrogen atom or alkyl group of 1-6 carbon atoms or aralkyl group of 7-10 carbon atoms;

the dotted line means an optional chemical bond;

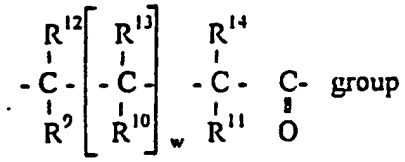
n is zero 1, 2 or 3;

X means-CH_2-group, -NH-group, carbon atom, hydrogen atom, oxygen atom, amino group; or

A means an R`- Y - N = group or R`-Y-N(R^9)- group - wherein R` means alkyl group of 1-6 carbon atoms, aralkyl group of 7-10 carbon atoms, diphenylmethyl group, alkoxy group , arylalkyloxy group of 7-10 carbon atoms, or phenyl- or phenoxy or phenylalkyl group containing 7-10 carbon atoms or phenylalkyloxy group containing 7-10 carbon atoms optionally substituted with halogen atoms or alkyl groups of 1-4 carbon atoms or nitro groups; Y means chemical bond or oxo-, sulfonyl- or sulfinyl group, R^9 means hydrogen atom or alkyl group of 1-4 carbon atoms; - with the proviso that in the case of formulas (20) and (33) X cannot mean - CH_2- group, -NH- group, oxygen atom or sulfur atom and in the case of formulas (30) and (31) X cannot mean - CH_2- group, oxygen atom or sulfur atom or amino group;

B means $-(CH_2)_m-C(=O)-$ group - wherein m is an integer of 1 to 21; or

$-O-(CH_2)_p-C(=O)-$ group wherein p is an integer of 1 to 3; or



group - wherein R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean independently from each other hydrogen alkyl or alkoxy group of 1-6 carbonatoms, halogen, amino group optionally substituted with one or two alkyl group of 1-6 carbonatoms; or

phenyl, phenoxy, aryl-alkyl group of 7-12 carbonatoms or aryl-alkoxy group of 7-12 carbonatoms each of them optionally containing 1, 2 or 3 same or different substituents identical to R^1, R^2, R^3 or R^4; or

two of R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean together an oxo or epoxy group or further chemical bond or four of them mean together two further chemical bonds and the remaining groups stand for hydrogen atoms; or

R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} mean together with the chain carbonatoms a saturated or unsaturated homocycle containing 3-8 carbon atoms or a saturated or unsaturated heterocycle containing 2-7 carbon atoms and a nitrogen or sulfur or oxygen atom, to which optionally an aromatic ring of 6-10 carbon atoms is condensed; and

w is zero or 1;

C means prolyl group or one of the groups of formula (37), or (38), (39), (40) or (41) - where n is 0, 1 or 2, Hlg means fluorine, chlorine, bromine, or iodine atom, R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group phenyl group or alkyl group of 1-4 cabonatoms or R^5 and R^6 together mean oxo-group; R^{16} means an alkoxy group of 1-4 carbon atoms, or -NH- CH_2 -CN group, or - NH- CH_2-CO_2R^7 group - where R^7 is defined as above; or

D or L structural unit or one of the group of the formula (42) or (43) - where the dotted line means a chemical bond optionally present or

a group of the formula (44) -wherein R^{15} means hydrogen atom, alkyl group of 1-6 carbon atoms, phenyl or naphthyl group; or

a group of the formula (45) - wherein Z means NH - group, oxygen atom or sulfur atom;

D means a covalent chemical bond or prolyl- or thioprolyl group; or

one of groups of formula (37) or (38), (39), (40) or (41);

L means pyrrolidino- or 2- cyanopyrrolidino, thiazolidino or 2-cyano-thiazolidino or piperidino group optionally substituted with one halogen atom or geminally with two halogen atoms; or

a group of the formula (46) - where R^{17} means hydrogen atom or cyano group, n is 0, 1 or 2 ; or

a group of the formula (47) or (48);

and optical , cis-trans, geometric isomers , epimers, tautomers, salts, prodrugs and human and mammalian metabolites of them.

(Priority: 17 August 1995)

8.) Compounds according to claim 7 - wherein

A means a group of the general formula (I) or (9) or (11a) or (11b) or (13) or (22) - wherein R means hydrogenatom alkyl group of 1-4 carbon atoms or aryl or aralkyl group of 6-10 carbon atoms,

R^1, R^2, R^3 and R^4 mean independently from each other hydrogen atom, halogen atom, hydroxyl group, straight chain or branched chain alkyl or alkenyl- or alkinyl or alkoxy- or alkenyloxy- or alkinyloxy groups containing 1-6 carbon atoms, nitro-group, amino group, monoalkylamino or monoacylamino group of 1-12 carbon atoms, dialkylamino- or diacylamino group of 2-24 carbon atoms - where the acyl group is an alkyl, aralkyl, cycloalkyl or aryl type -, cyano group, mercapto group, carboxyl group, esterified carboxyl group of 2-7 carbon atoms, hydroxyalkyl group of 1-6 carbon atoms, acyl group of 1-7 carbon atoms, acyloxy group of 1-7 carbon atoms, phenyl or benzyl group, anilino group, benzoyl group, phenoxy group, benzyloxy group, isocyanato group, isothiocyanato group, alkylthio group of 1-6 carbon atoms, sulfamino or sulfamoyl group, thiocyanato or cyanato group;

R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group or phenyl group or alkyl group of 1- 4 carbon atoms or R^5 and R^6 together mean oxo group;

R^7 means alkyl group of 1-6 carbon atoms;

R^8 means hydrogen atom or alkyl group of 1-6 carbon atoms or aralkyl group of 7-10 carbon atoms;

the dotted line means an optional chemical bond;

n is zero 1, 2 or 3;

X means-CH_2-group, -NH-group, carbon atom, hydrogen atom, oxygen atom, amino group;

B means a - $(CH_2)_m$ - $\overset{\overset{O}{\|}}{C}$ - group - wherein m is 2 or 3;

C means a prolyl group or a group of the general formula (38) or (41) wherein n is 0, 1 or 2;

D means a covalent chemical bond;

L means a pyrrolidino group - and optical, cis-trans, geometric isomers, epimers, tautomers, salts produgs and human and mammalian metabolites of them.

(Priority: 17 August 1995)

9.) Compounds according to claim 7 - wherein

A means a group of the general formula (1) or (4) or (9) or (11a)or (11b) - wherein

R means hydrogenatom, alkyl group of 1-4 carbon atoms or aryl or aralkyl group of 6-10 carbon atoms,

R^1, R^2, R^3 and R^4 mean independently from each other hydrogen atom, halogen atom, hydroxyl group, straight chain or branched chain alkyl or alkenyl- or alkinyl or alkoxy- or alkenyloxy- or alkinyloxy groups containing 1-6 carbon atoms, nitro-group, amino group, monoalkylamino or monoacylamino group of 1-12 carbon atoms ,dialkylamino- or diacylamino group of 2-24 carbon atoms - where the acyl group is an alkyl, aralkyl, cycloalkyl or aryl type -, cyano group, mercapto group, carboxyl group, esterified carboxyl group of 2-7 carbon atoms, hydroxyalkyl group of 1-6 carbon atoms, acyl group of 1-7 carbon atoms, acyloxy group of 1-7 carbon atoms, phenyl or benzyl group, anilino group, benzoyl group, phenoxy group, benzyloxy group, isocyanato group, isothiocyanato group, alkylthio group of 1-6 carbon atoms, sulfamino or sulfamoyl group, thiocyanato or cyanato group;

R^5 and R^6 mean independently from each other hydrogen atom, hydroxyl group or phenyl group or alkyl group of 1- 4 carbon atoms or R^5 and R^6 together mean oxo group;

R^7 means alkyl group of 1-6 carbon atoms;

R^8 means hydrogen atom or alkyl group of 1-6 carbon atoms or aralkyl group of 7-10 carbon atoms;

the dotted line means an optional chemical bond;

n is zero 1, 2 or 3;

X means-CH_2-group, -NH-group, carbon atom, hydrogen atom, oxygen atom, amino group;

B means a $-(CH_2)_m-\overset{\overset{O}{\|}}{C}-$ group - wherein m is 2 or 3;

C means a prolyl group or a group of the general formula (38) or (41) - wherein n is 0, 1 or 2;

D means a covalent chemical bond;

L means a pyrrolidino or thiazolidino group - and optical, cis-trans, geometric isomers, epimers, tautomers, salts prodrugs and human and mammalian metabolites of them.

(Priority: 17 August 1995)

10.) Pharmaceutical composition containing one or more compounds of the general formula (I) - wherein the meanings of A, B, C, D and L are as given in claim 7 - and/or optical, cis-trans, geometric isomers, epimers, tautomers, salts and prodrugs and human mammalian metabolites of them, alone or together with usual carrier and/or auxiliary materials applied in the pharmaceutical industry.

(Priority: 17 August 1995)

11.) A process for the preparation of compounds of the general formula (I) - where in the meanings of A, B, C, D, and L are as given in claim 7 - and optical, cis-trans, geometric isomers, epimers, tautomers and their salts, characterized in that a racemic or optically active carboxylic acid of the general formula (II) - where the meanings of A and B are as given in claim 7 - is transformed to an acid halide, or an active ester, or to a mixed acid anhydride or to a carbodiimide, and the resulted compound is reacted with a racemic or optically active compound or their salt of the general formula (III), - where the meanings of C, D and L are as given in claim 7 - and the resulted compound of the general formula (I) - where the meanings of A, B, C, D, and L are as given in claim 7 - optionally is separated into their optical, cis-trans, geometric isomers, epimers or tautomers or a salt of compounds of general formula (I) is formed, or the compounds of general formula (I) are liberated from their salts.

(Priority: 17 August 1995)

12.) A process according to claim 11 characterized in that, an acid addition salt of compound of general formula (III) is used.

(Priority: 17 August 1995)

13.) A process according to claim 11 characterized in that, a reactive mixed anhydride is formed starting from a compound of the general formula (II) and

pivaloylchloride is applied.
(Priority: 17 August 1995)

14.) A process according to claim 11 characterized in that, the reaction is carried out in an organic solvent.
(Priority: 17 August 1995)

15.) A process according to claim 11 characterized in that, the reaction is carried out at a temperature between - 25 °C and the boiling point of the reaction mixture.
(Priority: 17 August 1995)

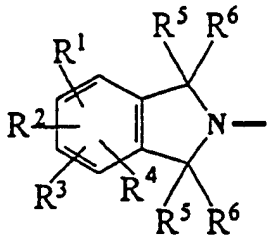
16.) A process according to claim 11 characterized in that, the reaction is carried out in the presence of an acid binding agent.
(Priority: 17 August 1995)

17.) Use of the compounds of the general formula (I) defined in claim 6 for inhibition of prolyl-endopeptidase enzime in mammals including man.
(Priority: 17 August 1995)

18.) Compounds according to claim 1 or claim 7 substantially as hereinbefore described.

A—B—C—D—L

[I]



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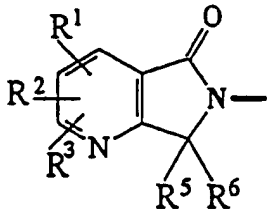

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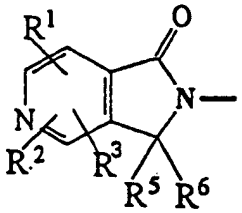

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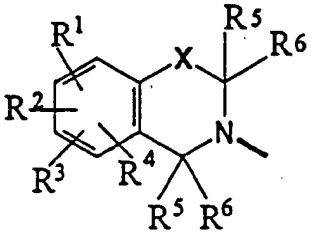

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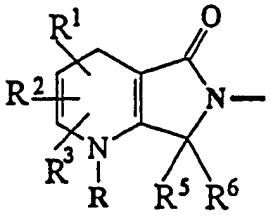

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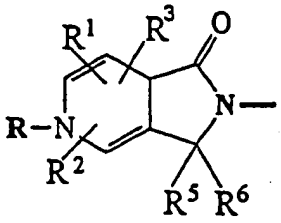

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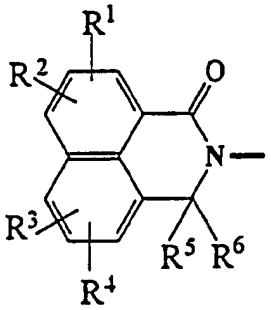

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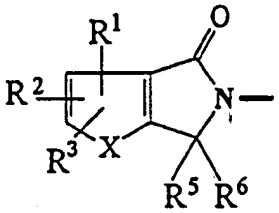

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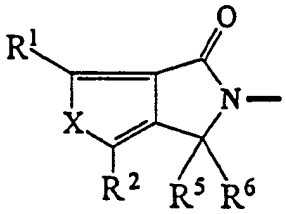

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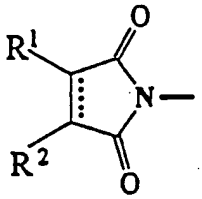

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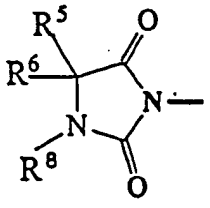

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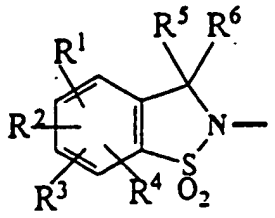

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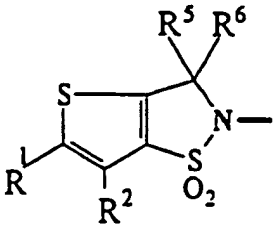

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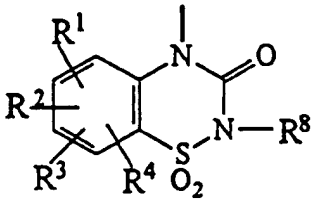

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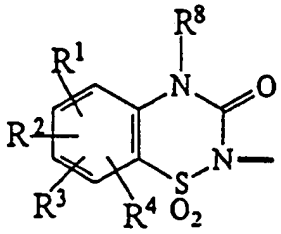

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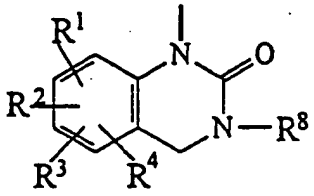

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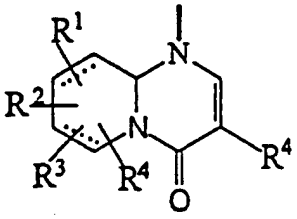

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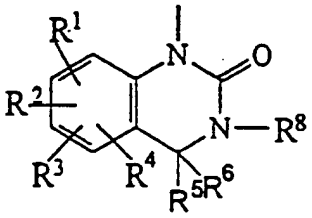

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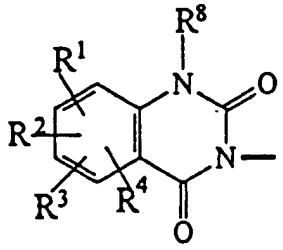

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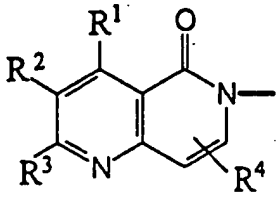

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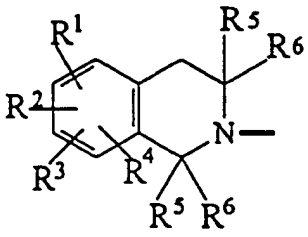

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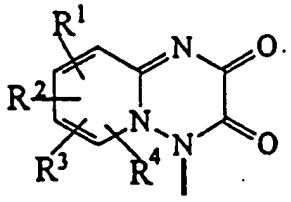

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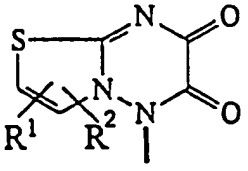

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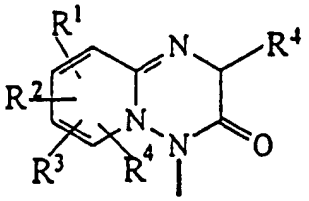

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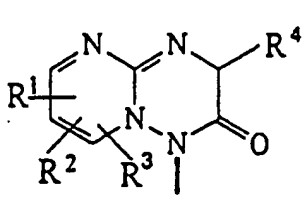

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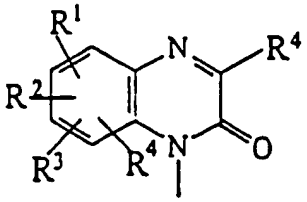

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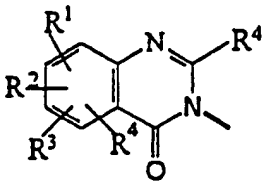

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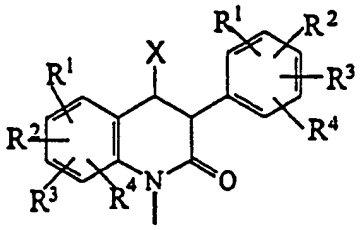

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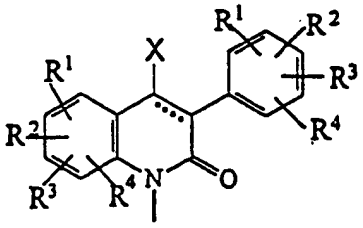

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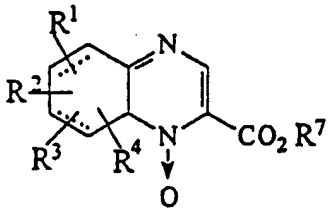

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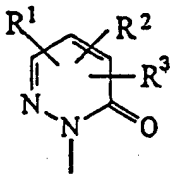

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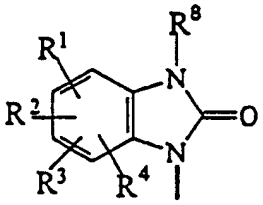

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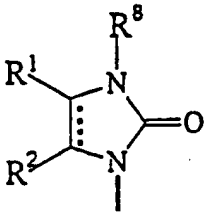

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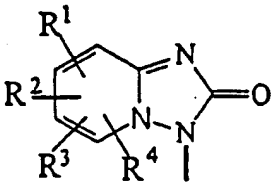

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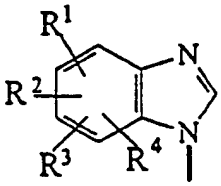

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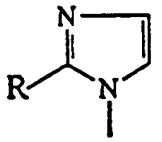

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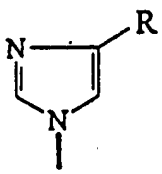

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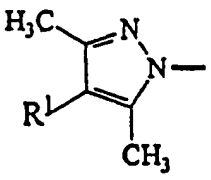

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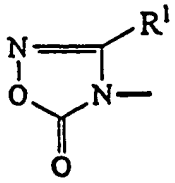

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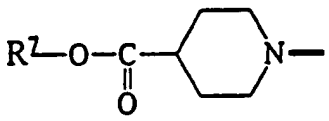

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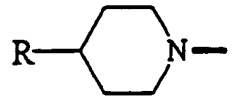

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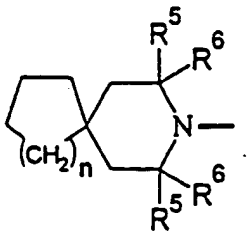

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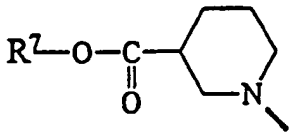

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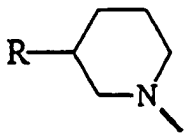

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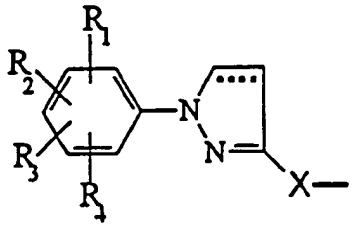

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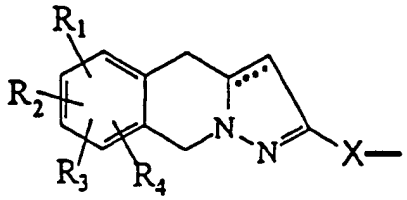

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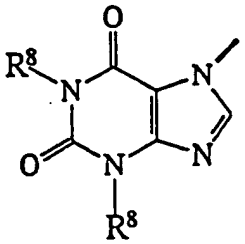

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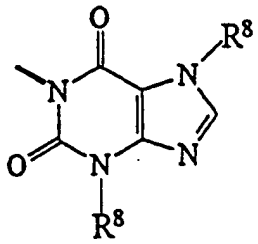

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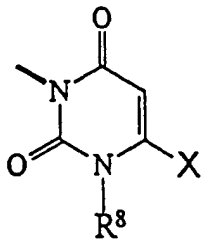

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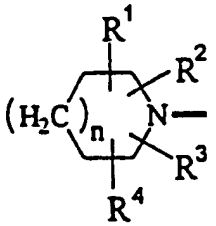

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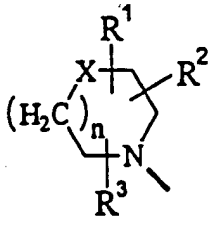

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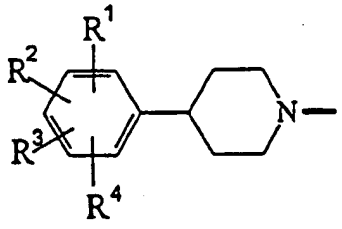

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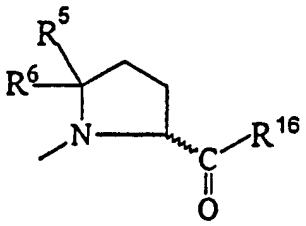

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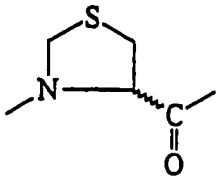

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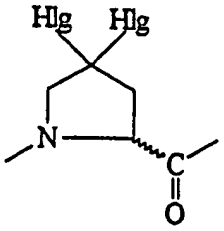

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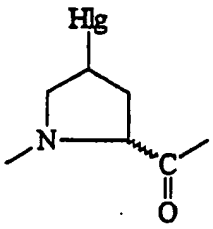

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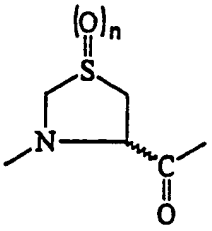

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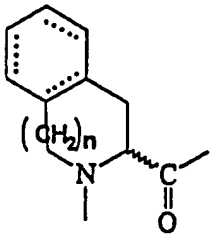

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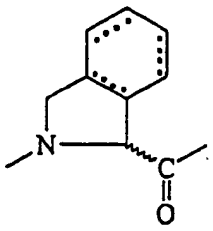

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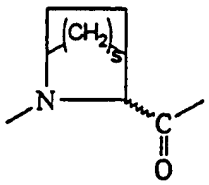

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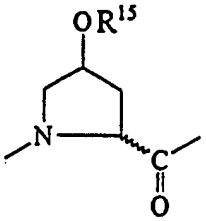

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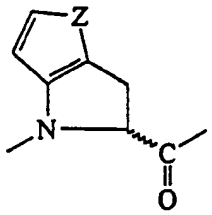

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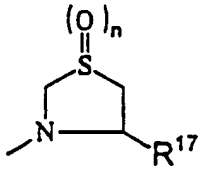

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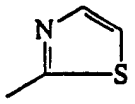

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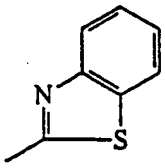

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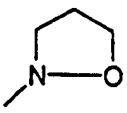

[49]

A—B—OH

[II]

H—CDL

[III]

INTERNATIONAL SEARCH REPORT

Interr tal Application No
PCT/HU 96/00041

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/06 A61K31/33 C07D401/14 C07D417/14 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 419 683 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 3 April 1991 see claims ---	1,4,6
A	EP 0 468 469 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 29 January 1992 see claims ---	1,4,6
A	EP 0 372 484 A (ZERIA PHARMACEUTICAL CO.,LTD.) 13 June 1990 see claims ---	1,4,6
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 13, - 1994 WASHINGTON US, pages 2071-2078, XP002022213 YOSHIAKI TANAKA ET AL: "New potent prolyl endopeptidase inhibitors: ..." see tables 1,2 -----	1,4,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 1997	17.01.1997
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 96/00041

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Please see attached sheet ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The vast number of theoretically conceivable compounds comprised under formula (I) of claim 1 precludes a comprehensive documentary search. Similarly the absence of (a) relevant fixed fragment(s) in the general formula (I) precludes a comprehensive on line search in a structure data base and would not be economically justified (cf. Arts. 6, 15 and Rule 33 PCT; see Guidelines B III 2.1).

INTERNATIONAL SEARCH REPORT

information on patent family members

Intern al Application No
PCT/HU 96/00041

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-419683	03-04-91	WO-A-	9012005	18-10-90
		US-A-	5118811	02-06-92
EP-A-468469	29-01-92	CA-A-	2048010	28-01-92
		JP-A-	5025125	02-02-93
		JP-B-	7108897	22-11-95
		US-A-	5506256	09-04-96
EP-A-372484	13-06-90	JP-A-	2262557	25-10-90
		JP-B-	8022847	06-03-96
		AT-T-	113279	15-11-94
		AU-B-	616824	07-11-91
		AU-A-	4591489	14-06-90
		CA-A-	2004028	08-06-90
		DE-D-	68919054	01-12-94
		DE-T-	68919054	11-05-95
		ES-T-	2065975	01-03-95
		US-A-	5028604	02-07-91